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ARTICLES ON COMMUNIST CHINA'S PROGRESS IN PHARMACOLOGY IN PAST DECADE

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## I. A DECADE OF ACHIEVEMENT IN RESEARCH ON

### CHINESE TRADITIONAL DRUGS

Following is a translation of an excerpt of an article by the Institute of Traditional Drugs, Research Institute of Chinese Traditional Medicine, in the Chinese-language periodical Yao-hsueh T'ung-pao (Pharmacology Bulletin), Peiping, Vol. VII, No. 9, September 1959, page 440.

#### Research on the Chemistry and Pharmacology of Chinese Traditional Drugs

In November 1954, the Jen-min Jih-pao printed an editorial under the heading "Intensify the Control and Research Work on Chinese Traditional Drugs." It said in part: "In order to raise the scholarly level of the Chinese traditional drug herbalist and the actual effectiveness of such drugs in therapeutics, research on Chinese traditional drugs must be intensified. The purpose of such research seeks to support the effective therapeutic property of such drugs with scientific explanations to further master such drugs and to assure the accuracy of drug use in prescriptions. Furthermore, new uses are to be found for existing drugs, so that the contents of pharmacology may be substantiated, and its level raised. Intensifying scientific research on Chinese traditional drugs has a great effect on work to revise the mode of drug prescription." This clearly states the necessity for scientific analysis and tests to be done on Chinese traditional drugs, but such work must be coordinated with clinical use and have therapeutic effectiveness as the highest standard. In the field of chemical research, some results have been obtained during the past few years. From the standpoint of extraction and study of the effective components in Chinese traditional drugs, research studies have been conducted on a number of traditional drugs such as the Ginkgo biloba, L. seed Coccus, Quisqualis indica, L., Typha latifolia, Coptis chinensis, DC, Aconitum Fischeri, Brucea javonica, L., tangerine peel, almond, Stemona japonica, Miq., Fritillaria verticillata, Anemone chinensis, Bunge, blossoms of Sophora japonica, L., Inula Helenium, L., Conioselinum univittatum, Turcz, peel and root of Sapium Sebiferum, Roxb., etc.;. On some of them, crystalline extractions have been possible and their chemical formulas have been determined. On the amount of effective components contained in Chinese traditional drugs, pharmacology workers in China have used chemical methods to conduct some studies with definite results which are available for reference in a forward step to change the mode of drug prescription and analysis in clinical effectiveness.

Research on the anti-bacterial action of Chinese traditional drugs has also undergone great development during the last few years. Experiments on the anti-bacterial action of several hundred traditional drugs against gram positive bacteria, gram negative bacteria and fungi in vitro show rhubarb and Coptis chinensis to have a bacteriostatic effect against the

*Staphylococcus aureus*; *Coptis chinensis* to also have a bacteriostatic effect against the *Bacillus dysenteriae*, and the *Mycobacterium tuberculosis*, var. *hominis*; *Allium scorodoprasum* to have a bactericidal effect on most disease causing bacteria, and the *Forsythia suspensa* and *Lonicera japonica* [?] to have a fairly large anti-bacterial application.

As for pharmacology in general, most of the experiments have been limited to research on simple one ingredient drugs. For instance, the Tsingtao Medical College (1955) discovered the contracting effect of tumeric on the uterine muscles and followed it up with the contracting effect (1955) of carthamus and saffron on the uterus. This same college (1956) also proved the effect of licorice on tetanus toxin by experiment, and its effectiveness is increased when used in conjunction with turpentine. At the same time the slight antidote action of licorice against cocaine was also proven. The teaching and research unit on pharmacology (1955) at Wuhan Medical College progressed a step and proved the analgesic properties of *Corydalis ambigua*. The pharmacology division of the Chinese Academy of Medical Science (1956) observed the hypotensive effect of many Chinese traditional drugs by the experimental therapy method and discovered that *Conioselinum univittatum* taken orally cures induced hypertension in animals. This division (1957) also discovered components in *Justicia gendarussa*, L. have the effect of relieving induced arthritis in animals. The Institute of Traditional Drugs of the Research Institutes of Chinese Traditional Medicine (1955) used the animal experimentation method to prove that bezoar and its synthetic substitute manufactured by the Tientsin Pharmaceutical Works both have anti-epileptic properties. This has resulted in a solution to the problem of bezoar supply and has helped the national government save on its foreign exchange. This institute (1956 - 1957) also studied an antispasmodic powder used in the treatment of epidemic Type B meningitis. This is made from a combination of powdered centipede and whole scorpion. Experiment results show that this powder combination has an antispasmodic effect on animals when taken orally. In conditional reflex experiments on white mice, this centipede and whole scorpion drug is seen to reduce the degree of stimulation and increase the powers of self control in higher nervous system activity of animals. This phenomenon is even more obvious when taken orally. The Second Army Medical College of the Chinese People's Liberation Army has also been conducting coordinated research on *Veratrum Nigrum*, L. to treat schistosomiasis and extracted components from the leaves of *Orixa japonica*, and Thunb. for intravenous injection into white mice to test their hypotensive effect. The Seventh Army Medical College has been studying the effectiveness of *Pinellia tuberifera*, Ten. in relieving nausea and reducing saliva secretion. Comparative observations on the effect of *Aconitum Fischeri* in its decocted and crude forms have also been made. Results show that the toxicity of *Aconitum Fischeri* is reduced after decoction which explains the fact that this method of traditional Chinese medicine is a scientific one.

## II. CHINA'S ACHIEVEMENTS IN PHARMACEUTICAL CHEMISTRY

[Following is a translation of an article by Liu Wei-ch'in, Meng Mu-ti, Liang Hsiao-t'ien, Shen Chia-hsiang, and Ch'en Hsin-lien in the Chinese-language periodical Yao-hsueh T'ung-pao (Pharmacology Bulletin), Peiping, Vol. VII, No. 9, September 1959, pages 442-444.]

### I.

Due to the emphasis placed on it by the Party and the government since the Liberation, research in pharmaceutical chemistry has seen rapid development on an overall scale. Whether it be on a synthetic chemical compound or natural medicine, the valuable work done in theoretical research had laid a good foundation for long range research and further research in traditional Chinese drugs for now and the future. In research on synthetic chemicals which has serving production as its direct goal, the findings have impelled China's pharmaceutical industry with such great force to result in great accomplishments. In recent years, chemical research into plants as drug sources has also been initiated. Much of the research in pharmaceutical analysis has stimulated raising the technical level of pharmaceutical inspection and contributed many basic scientific findings for the new edition of *Pharmacopeia Sinica*.

As the field covered by this article is quite extensive, only the more spectacular examples are used for further clarification in the following paragraphs.

### II

One of the glorious tasks of the pharmaceutical research worker is searching for effective new drugs to eradicate diseases endangering the people's health. Therefore, the first consideration of theoretical research in pharmaceutical chemistry is the creation of safer and more effective pharmaceutical chemicals for the prevention and treatment of serious diseases. Due to the fact that schistosomiasis is prevalent over a large area seriously endangering the people's health, and that fact that tartar emetic which is the therapeutic agent most widely used has many disadvantages, related research agencies in the nation have exerted much research effort in this direction for many years. More than a thousand compounds with or without antimony in them have been made. Of these, more than 400 have passed screening selection tests and more than 100 of them have been subject to tests in therapeutical research and pharmacological studies. The few with more effective action have been tried clinically<sup>(1)(2)</sup>. For example, from antimony derivatives in a series of thiolates, antimony potassium dithiosuccinate and antimony potassium 2,5-dithiocadipate were found to be more effective than tartar emetic<sup>(3)(4)</sup>. From the salts of an antimony gluconate series, antimony ammonium trigluconate was found to show less reaction than tartar emetic, and the recurrence rate after treatment was lower<sup>(2)</sup>. Besides these, many effective oral antimony compounds such as pyroantimonite-pyrimidine<sup>(1)</sup> which is less toxic than tartar emetic, were found. At the same time, some achievement has been obtained on

research into dissolving enteric coatings and dissolving gelatin capsules used in the making of enteric pills<sup>(5)(6)</sup>. From a series of aromatic antimony compounds, p-oxytibine phenyl thioacetic acid [sic] and its ethyl derivative are both found suited for oral use. Furthermore, preliminary clinical trial of the latter showed a smaller reaction and a better therapeutic effect. Testing on it is continued<sup>(7)</sup>. In compounds not containing antimony, research is directed chiefly on derivatives of amino-oxybenzene paraffins, rose phenylamines, deoxygenated benzoids and other mixed compounds<sup>(1)</sup>. However, a compound with an outstanding therapeutic effect is yet to be found from them.

In other types of therapeutic chemicals, research into anti-tuberculosis drugs has been directed toward the hydrazides, and a preliminary investigation has been initiated to determine the relationship between their chemical structure and their bacteria resisting action<sup>(8-17)</sup>. There is also research on the synthesis of chloramphenicol "analogues" which started from the premise that the creation of metals controlled cycline compounds is possibly related to anti-bacterial action, thereby forming a series of o-hydroxy- phenyl propyl ketone derivatives. Testing of their anti-bacterial effect shows compounds with structures controlled by a hydrogen key to have a stronger bacteria resisting effect<sup>(18-22)</sup>.

Research on hypotension inducing oral saccharide drugs must also be mentioned. In 1958, China utilized para chloropheno-sulfonic acid which is a byproduct of DDT to form a series of para chloropheno-sulfocarbamides and discovered their good pharmacological effect<sup>(23)</sup>. At present, theoretical research on this continues.

Because of firm adherence to the principle of "self-transformation" under the correct leadership of the Party whereby great effort is directed toward development of raw material drugs, the accomplishments of China's pharmaceutical industry during the past ten years are outstanding. The total amount of drugs produced through chemical synthesis and variations in drug types has increased by leaps and bounds. Capital expenditures and waste of raw materials continue to be lowered, while the production efforts of the workers continue to be raised. All this indicates a basic change in the backward picture of the old China of the past which depended on importing raw materials for simple processing. The rapid development of industrial construction at the same time expresses the contribution of scientific research toward production. Because of direct efforts toward production, research on the chemical synthesis of drugs has been very successful. These efforts have covered various aspects in the experimental manufacture of new products, research on new methods of chemical synthesis, great improvements in production techniques, etc. Focus of research in the chemical synthesis of drugs is placed on antibiotics, synthetic drugs with special effects, and other related types that all have an important bearing on assuring the health of the nation's people.

Where synthetic antibiotics are concerned, research on chloromycetin synthesis was initiated not long after the founding of the state<sup>(24)</sup>. Following that, in coordination with the actual raw material supply conditions in China, the production course utilizing nitroethyl benzene was studied with success and put into effect. By 1955, this method was thrown into volume production<sup>(25)</sup>. For the last three years continued research on the chemical synthesis of chloramphenicol has seen the oxidation method of transforming p-nitroethyl benzene into p nitro acetophenone effected in production while many other improvements in techniques have also been made<sup>(26-32)</sup>. In the three years covering the period from 1956 through 1958, the technological and production level of all the workers continued to rise to result in savings of more than 30,000,000 yuans in capital expenditures<sup>(33)</sup>. Much research related to the chemical synthesis of chloramphenicol was also carried out<sup>(34-41)</sup>. Among this were studies of new ways of synthesis<sup>(38-41)</sup>. Besides this, a new antibiotic called cycline amino acid was also successfully synthesized in 1958, and its production on a small scale was initiated<sup>(42)</sup>.

As for research on the sulfonamide drugs, emphasis has continued to be placed on it during the past few years, and the production capacity of these drugs has made great strides. At present, an economical method for the industrial production of sulfadiazine drugs has been partially settled<sup>(43)</sup>, and many new types have been successfully manufactured<sup>(44)</sup>. Research in these two aspects must be continued in the future.

The chief course of this continued rise in the technological level is the centered around the technological revolution mass movement to economize and increase production. The central laboratories in the plants and the great number of workers have both effected great improvements in production techniques. On one hand are simplification and shortening of the working process and economical use of materials as seen in the appearance of many direct condensation methods such as the direct condensation of isonicotinic acid with a hydrazide to form isoniazid<sup>(45)</sup>, the direct condensation of ethylene chlorohydrin and chlorobenzene to form DDT<sup>(46)</sup>, the direct condensation of dicyanamide and sulfanilamide in the presence of amide(s) to form sulfamidinum<sup>(47)</sup> which has a high production capacity. On the other hand, are the returns and coordination utilization of many materials as seen from the returns with most of the by products in the production of sulfathiazole and phenacetin at present, which results in hardly any matter wasted. Furthermore, due to the fact that China can make many kinds of synthetic drugs at the moment, the production and experimental manufacture of anti-tuberculosis drugs, anti-malarial drugs, various antimony compounds, and cancer arresting drugs, the volume production of antipyretics, and the experimental manufacture of many new synthetic drugs with strong physiological effects show up in many respects with the research results of an industrial reform nature.

China is rich in natural resources. Much work has been done in the research and utilization of natural drugs. Somewhat more significant is the coordinated research being done on China grown *Rauwolfia verticillata* which covers research on the alkaloid content found in the root and leaf of *Rauwolfia verticillata* and their respective alkaloid composition<sup>(48,49)</sup>, and research on the composition makeup of other related plants<sup>(50)</sup>. After a systematic analysis and comparison of *Rauwolfia verticillata* grown in various areas of China and a pharmacological study of the isolated alkaloid to determine its therapeutic effect on hypertension, it has been put into clinical use. Reserpine has been successfully extracted from the root of *Rauwolfia verticillata* and it is now made on a production basis. Besides this, improved extract processing of the ephedrine alkaloid, successful study of an economical method to transform pseudo ephedrine alkaloid into ephedrine alkaloid<sup>(51,52)</sup>, improved methods of santonin extraction and analysis<sup>(53-57)</sup>, changes in the production method to extract digitoxin<sup>(58)</sup> all have a very great effect on industrial production. In the field of theoretical research, systematic studies have been made on peimine<sup>(59)</sup>, the plant composition of *Cocculus diversifolius*, Miq.<sup>(60-63)</sup> and *Aristolochia*, L.,<sup>(64-66)</sup> the chemistry of the flavanoids<sup>(67-69)</sup> found among traditional Chinese drugs, and contributions have been made in the field of solid chemistry pertaining to santonin<sup>(70-71)</sup>. Studies on the chemical composition of *Strophanthus divaricatus* (Lour.) (Hook et Arn)<sup>(72-74)</sup>, *Salsola ruthenica*<sup>(75)</sup>, etc. have also been made.

Achievements in the industrial synthesis of natural matter has set a new mark on the development in China's pharmaceutical industry and the people's economy. During the past two years, actual results have been obtained in studies to produce caffeine through chemical synthesis which starts with the condensation of cyanoacetic ester and urea through a total of only four steps<sup>(76)</sup>. In the industrial synthesis of vitamins, research on the experimental manufacture of all the important B family vitamins that can be produced through chemical synthesis at the moment has been completed. Of these, Vitamin B<sub>1</sub><sup>(77)</sup>, pantothenic acid<sup>(78)</sup>, and folic acid<sup>(79)</sup> are being produced in small amounts, and the experimental manufacture of Vitamins B<sub>2</sub> and B<sub>6</sub> is also completed. Only Vitamin B<sub>12</sub> is still obtained through extraction<sup>(80)</sup> in amounts that meet the national need now. A large sized processing laboratory for the synthetic manufacture of Vitamin C has been in existence for some time. In the manufacture of oil soluble vitamins, the techniques for the chemical synthesis of crystalline Vitamin A acetic esters have been mastered<sup>(81)</sup>. The experimental manufacture of crystalline Vitamin D has also been successful. Since 1958, development of research on the chemical synthesis of stereo-hormones also swung up. In the past year, places growing steroid plants were sought for in a large scale, and the results of the survey showed that the raw material factor is in China's favor. From wild plants of the *Dioscorea* family<sup>(82-83)</sup> found over an extensive area, valuable diosgenin may be extracted. From the waste liquor of the chien-ma industry a great quantity of hecogenin can be returned. From *Anemarrhena asphodeloids* Bunge, sarasapogenin is extracted.

From *Yuca Filementosa* L. (84), gitogenin and tigogenin are extracted. From the byproduct resins of paper manufacturing the salvage of  $\beta$ -Sitosterol (85) is also being studied. All these are convenient raw materials used in synthesizing the steroid hormones. At present, separate utilization of diosgenin or hecogenin has resulted in the successful synthesis of compounds such as cortisone, cortisol,  $\Delta^1$ -dehydrocorticosterone,  $\Delta^1$ -dehydrocortisol (86). These methods of synthesis are going through intermediate scale tests before gradual application on a production basis. Corpus luteum hormone, testosterone, methyl-testosterone, etc. have been formally thrown into production.

Research on raw material substitutes which are found from natural resources and used in the manufacture of drugs has also shown some progress in recent years. Examples are the substitution of the esters of *Sapium Sebiferum*, Roxb. (87) and *Coniselinum univittatum*, Turcz. (88) for the ester of cocoa bean and the substitution of the gums of *Bletilla hyacinthina*, Rohb. F. (89) and the seeds of *Plantago major*, L. var, *asiatica*, Dcne. for Arabic gum.

Research on pharmaceuticals made from hormones provided by animal sources has also been conducted in recent years. At present, important hormones such as insulin, pitocin, ACTH etc. are being manufactured on a production scale (90).

In order to assure the safety and effectiveness of the drugs being used by the people, the Chinese government places great emphasis on the regulations pertaining to inspection, standardization and certification of drugs. The advanced level of pharmacological techniques analysis used in China in recent years is expressed in the wide scale application of certain modern analysis techniques. For instance, the paper layering analytical method has been used in the determination and certification of Chinese traditional drugs and some studies have also been made on the method of paper layering analysis as applied to aureomycin (91). Besides being used to measure metal ions, polarographic analysis may also be used to determine sex hormones (92), and streptomycin (93). The method of paper electrophoresis has been used in the investigation of non-volatile toxic matter. Furthermore, in the applications of the colorimetric method (94-96), the non-water soluble spot method (97-110), and the combined spot method (111-115), much research has also been conducted. Due to the large scale use of organic antimony compounds to treat bilharziasis, the methods to determine and measure antimony also has undergone a series of detailed studies (116-120).

In coordination with production, the chemical analysts of drugs have also conducted much research on the analysis and controls of intermediate bodies in synthetic drugs (121-126), and studies and analysis of the effective components of Chinese traditional drugs (127-131). They have also put much effort into studies on quick methods of drug analysis, and have made a definite contribution toward quality determination of pharmaceuticals.

For the new 1959 edition of Pharmacopeia Sinica, pharmacological workers and pharmaceutical testers have done a great amount of research and testing which includes all chemical determination methods and the correlation and correction of impurities, and the study and selection of quantity determination methods suited to the actual conditions in China. In certification of biologicals, national standards that cover heparin, ACTH, etc. have been established during the last few years, and the biological determination methods for digitoxin<sup>(132)</sup>, pituitrin<sup>(133)</sup>, insulin<sup>(134)</sup>, ACTH<sup>(135)</sup>, heparin<sup>(136)</sup>, Vitamin D<sup>(137)</sup> etc. have also been revised and improved upon. Such work raises the scientific level of the new edition of Pharmacopeia Sinica.

### III

From the above, it can be seen that the work of China in pharmaceutical chemistry during the past ten years has reaped outstanding achievements. These achievements come from the mutual efforts of scientific technical workers and the large mass of workers throughout the nation. At the same time, this is also the result of the unselfish technological assistance given China by the various socialistic brother nations headed by the Soviet Union. In looking back on the achievements of the past ten years, we are deeply grateful for this unselfish assistance. The history of planned research in pharmaceutical chemistry in China is short, and continued learning from the Soviet Union and other brother nations is still needed to advance another step in coordinated research to find effective pharmaceuticals to treat tumors, diseases of the cardio-vascular system, radiation sickness, toxic diseases, and functional diseases of the nervous system. Furthermore, pharmacology in China must be regarded as a great treasury rich in content. We believe that through using the pharmaceutical chemistry method to continue regulating this treasure will result in still greater contributions for the science of medicine and pharmacology.

### III. CHINA'S ACHIEVEMENTS IN ANTIBIOTICS RESEARCH AND PRODUCTION

Following is a translation of an article by Chang Wei-shen of the Institute of Antibiotics, Chinese Academy of Medical Sciences, in the Chinese-language periodical Yao-hsueh T'ung-pao (Pharmacology Bulletin), Peiping, Vol. VII, No. 9, September 1959, pages 446-448.

The science of antibiotics only developed during the 40's of the twentieth century. At that time, China was going through the war of resistance when a strain of penicillin was grown in Kunming. Furthermore, the crude penicillin that was produced from this strain was considered to be of fair quality at the time. However, the reactionary government never considered scientific research as important, so there was no way for this research to develop further. Conversely, medical workers with the Eighth Route Army located in the area of the Tai-hang Shan also found penicillin growing spores under difficult conditions governing techniques and facilities. Due to the importance and support given it by the Party, the culture liquor was used to immerse gauze dressings in so that many wounds healed rapidly.

In 1949 after the whole nation was liberated, organizations were set up rapidly in Peking and Shanghai under the leadership of the Party to develop the production and research of antibiotics from nothing. In 1955, the National Committee on Antibiotics was formed and the needs of scientific research on antibiotics and the direction of the close coordination between production and application were defined. In order to increase coordination and assure cooperation, area working committees were set up separately in Peking and Shanghai. In 1956, a New Antibiotics Screening Section was set up under the National Committee on Antibiotics. This section was to carry out the direction of research and create a favorable climate for the establishment of actual rules and regulations to go with the coordination of activities.

In 1951, at the Antibiotics Laboratory of the Peking Institute of Research on Biological Products, the experimental manufacture of penicillin was successful and it was possible to produce it in small amounts. At the time, corn broth which was a basic ingredient used in the fermentation medium was not available in China, and its supply depended completely on foreign sources. In order to solve this difficulty, Chang Wei-shen and others from this research laboratory conducted research on corn broth substitutes in 1952, and discovered that cottonseed meal cakes could be used instead of the imported corn meal. The Third Pharmaceutical Plant of Shanghai experimented with cottonseed meal as the culture medium and produced penicillin from it. At the same time, this laboratory produced potassium salt crystals of penicillin to replace the illdefined sodium powder in penicillin so that some of the pain experienced by the patient during injection is reduced. In 1954, Huang Ta-pin et al of this laboratory further used the method of constant steam distillation to obtain well formed potassium salt crystals of penicillin. Production of penicillin

developed rapidly then except for the difficult supply of lactose which was another important ingredient used in the fermentation medium. In 1954, research by this laboratory found a way to use corn flour instead of lactose, so that fermentation of penicillin was able to use only native materials without resort to foreign imports.

The Third Pharmaceutical Plant of Shanghai was remodelled from an auto repair shop that existed before the Liberation. However, it expanded rapidly, and all of its equipment and facilities were built up gradually by Chinese technicians who put much effort into it. This plant was the first one in China to produce crystalline potassium penicillin and procaine penicillin to partially meet medical needs. During the course of procaine penicillin production, product quality continued to be raised to find suitable conditions. Before crystallization of product, a tiny seed crystal was introduced to result in most of the procaine penicillin crystals measuring less than 5 microns which made them suitable for intramuscular use. In 1959, Yu Li et al of the Third Pharmaceutical Plant of Shanghai carried out penicillin fermentation in a 5000 liter capacity fermentation tank where the chief ingredients of the culture medium were corn flour and powdered peanut cake. After 40 hours, dextrose was added 0.06 - 0.08%/hour. The effectiveness value of penicillin produced after 72 hours in this medium averaged 17% higher than that produced in a culture medium of lactose. The capital outlay was also lowered by 59.15%. Should the period of fermentation be extended to 84 hours, the amount of penicillin produced could be increased.

Toward the end of 1957, construction of the Hua-pei Pharmaceutical Plant was completed. This was a combined undertaking with antibiotics production as its central objective, and it was one of the focal construction items of China's first Five Year Plan. By 1958, it was thrown into production completely. Establishment of the Hua-pei Pharmaceutical Plant marked a new phase of grand scale operation and modernization that China's antibiotic industry had entered into. During construction of this plant, the Soviet Union and democratic Germany gave their unselfish assistance. This plant is made up of three units - an antibiotics plant, a starch factory and a glass factory. At present, the chief products are penicillin, streptomycin, vitamin B<sub>12</sub>, starch, dextrose etc. The corn steep liquor which is a by-product of the starch factory is one of the chief raw materials used in antibiotics production, and the glass factory supplies the small glass vials used to package the prepared antibiotics. The most advanced kinds of mechanical and automatic equipment are used for production at this plant. Examples are the glass drawing cylinder and bottle maker in the glass factory, corn selectors and storage bins in the starch factory, the latest turbine air compressor in the powerhouse of the antibiotics plant, the multi-staged steam spray pump used in vacuum packaging, film type vacuum condenser used in vacuum condensing also in the antibiotics plant.

When the equipment and machinery were being tested, the Soviet specialists and the Chinese technicians cooperated closely and worked day and night so that this plant was able to go into production rapidly. After this plant had been thrown into production, its output was able to meet the national needs for penicillin and streptomycin. Due to diligent research by the technicians at the plant here, the gluten of the corn steep liquor was used instead of the corn liquor, and resulted in raising the effectiveness value of penicillin to 5000 units/ milliliter. For this reason, the production volume of 1959 increased more than one time that of 1958.

The Antibiotics Research Laboratory of the Peking Institute of Research on Biological Products was reorganized in 1956 to come under the Chinese Academy of Medical Sciences where it was expanded into a Department of Antibiotics. Many new laboratory units were gradually added in the department, so that by October 1958, the department was expanded into an institute which became a more or less complete research framework embracing 12 different departments with an increase of more than twice the personnel it used to have. Since 1956, under the guidance of Soviet specialist, Professor Lieh-wei-t'o-fu, the problem pertaining to ways of penicillin synthesis has been studied. It is now discovered that during its early period of growth, the *Penicillium notatum* produces penicillin at the same time. It is possible that this discovery has provided a valuable approach toward biochemistry of the *Penicillium notatum* and the production of penicillin. The mechanics as to how *Penicillium notatum* utilizes the raw materials of starch has also been studied. Preliminary results show that *Penicillium notatum* does not contain any phosphorylase, that its water soluble starch goes through the amylase forming process, that the activity of amylase is more pronounced in fermentation liquor, but the action of maltase is comparatively weaker. The biosynthesis curve and pH changes of penicillin from starch culture media is similar to those of penicillin from lactose culture media, but growth curve of filaments on *Penicillium notatum* resembles growth curves of those from dextrose or malt culture media closely. Research at present, has advanced another step.

Research on the experimental manufacture of streptomycin began in 1953. After strain selection of spores and improvements made on culture media by the Antibiotics Research Laboratory of the Institute of Research on Biological Products, the effectiveness value of the fermentation liquor was raised from 100 - 200 units to 700 - 800 units. On the base of new spore strains obtained from the Soviet Union, the Shanghai Research Institute of the Drug Industry gradually raised this level to 4000 units per milliliter. At the same time, because of the need to refine streptomycin, research on Type "ABC" positive ion exchange process was successful. By this resin process, better quality streptomycin phosphates are obtained. This method has been turned over to the Hua-pei Pharmaceutical Plant for large scale production.

In research on streptomycin, Wang Yu et. al. of the Institute of Organic Chemistry of the Chinese Academy of Sciences isolated dihydrostreptose contained in streptomycin in a preliminary experiment and conducted comparisons on the oxygen metabolism of mutated cells of streptomycin dependent *B. coli* grown in culture media containing and not containing streptomycin. Results show that cells grown in medium without streptomycin obviously have a lower viability in relation to oxidation by dextrose, pyruvic acid, succinic acid, malic acid and lactose, fermentation by dextrose, release of oxygen in hydrogen peroxide, etc. than that grown in medium containing streptomycin. Falling energy metabolism possibly is one cause of abnormal growth in dependent *B. coli* growing in a medium not containing streptomycin.

Toward the production of aureomycin, Shen Shan-chiung et. al. of the Institute of Plant Physiology of the Chinese Academy of Sciences investigated the physiology of the *Streptomyces aureofaciens*. They discovered that the composition of the *Streptomyces aureofaciens* spore medium and its pH value have a great effect on the production of aureomycin during the fermentation process. In 1956 they proved that the iron ions did not hold back the biosynthesis of aureomycin, but the cause for a low effectiveness value aureomycin culture liquor from fermentation in a steel tank was due to the clumping together of the iron ions and aureomycin which made it hard to perform an assay. They discovered that the addition of triaminoacetic acid to this type of culture liquor will release the aureomycin. In 1956, Shen and group investigated the effect of phosphates on the sugar utilization of *Streptomyces aureofaciens* and the synthesis of aureomycin and pointed out the fact that an excessive concentration of phosphates in the culture medium will hasten the oxidation of sugars by the streptomycetes and deter the synthesis of aureomycin. In 1957, they proved the existence of an alternate metabolism course in the sugar metabolism picture of *Streptomyces aureus* which goes through the process of hexokinase. While such research hasten the production of aureomycin on one hand, it also adds to the knowledge on the physiology and metabolism of disease fighting fungi.

On the chemistry of aureomycin Huang Yao-tseng initiated a series of descending solution studies. Dehydrogenation and de-dimethylaminization of zinc powder and acetic acid and the dehydration of hydrochloric acid will result in many dehydrogenated and zinc hydrolyzed products. These compounds often will become tetraphenes after zinc powder distillation. All of this serves to prove the carbon structure of aureomycin. Tung Hung-yun et al also used the alkali process on de-dimethylaminized aureomycin to obtain de-dimethylaminized iso-aureomycin. The latter may also be obtained from iso-aureomycin undergoing powdered zinc and acetic acid action, and the broken down products etc. which cannot result in cotetraphenyl during the powdered zinc distillation process or thermal decomposition in vacuum will produce 3-methyl-4-chloro-7-hydroxy-1-kets - isobenzodihydrofuran instead.

By catalyzed hydrolysis of dehydroaureomycin with 10% palladium carbon, Huang Yao-tseng et. al. were able to obtain dechlorinated dehydroaureomycin that is like that obtained by other methods as described in medical articles. Giving the same treatment to de-dimethylaminized aureomycin and de-dimethylaminized dehydroxy-aureomycin, corresponding dechlorinated products may be obtained.

During the intermediate stages of research on the experimental manufacture of aureomycin, the Shanghai Research Institute of the Medical Drugs Industry was making spore selections and cultures in an endeavor to raise the production amount of aureomycin, and they were able to obtain a spore strain capable of producing 6,700 units/liter. Furthermore, this research institute improved on the method of extracting aureomycin by using the solvent extraction method to replace the complicated method of precipitation with calcium salts so that work efficiency and the extract returns are both increased.

In 1955, the Antibiotics Research Laboratory of the Institute of Research on Biological Products began the experimental manufacture of terramycin by using spore strain 8229. In 1957, the Department of Antibiotics of the Chinese Academy of Medical Sciences made physiological and biochemical studies on terramycin spore strain 8229, and discovered the addition of lactose to the culture media will result in a more than one time increase in the effectiveness value. Later on, a new spore strain *S. rimosus* ER obtained from the Soviet Union was placed in a fermentation tank of 110 liter capacity to ferment and the resulting effectiveness value reached 3,950 units/milliliter. Recently, the Shanghai Research Institute of the Medical Drugs Industry expanded the experimental production of terramycin, and the effectiveness value was raised to a figure exceeding 6,000 units. At present, this institute has changed over to the method of extracting terramycin with butanol which is much simpler than the precipitation method used in the past, and the rate of returns is also much higher.

Studies on the experimental manufacture of neomycin by the Shanghai Research Institute of the Medical Drugs Industry have also been completed and ready for production. At the same time, this institute also carried out studies on the experimental manufacture of tetracycline by adding sodium bromide and 2-mehcapto-1, 3-dibenzothiazole to the fermentation media, thereby causing the *Streptomyces aureus* to produce tetracycline prolifically. Furthermore, after screening and selected culture of spore strains, the effectiveness value of fermentation has been increased to 6,500 units/ milliliter.

The Institute of Antibiotics of the Chinese Academy of Medical Sciences only spent four months in 1958 to complete the experimental manufacture erythromycin. Due to mastery of the controls on the incubation period for spore culture and fermentation ingredients, effectiveness value has been increased. The extraction method has also been improved upon, and complicated pressure reducing and condensing processes have been eliminated. Not only is the production capital outlay reduced, production facilities are also simplified. Tetracycline just described and erythromycin are both produced in small amounts now.

Syntomycin was produced in the Industrial Chemistry Laboratory of the Ministry of Industrial Chemistry at a very early date. It is synthesized chemically, and recently syntomycin has been separated with tartaric acid into levomycetin (which is chloromycetin).

In 1947, Wang Yu et. al. made some studies on the antibacterial effect of citrinin and discovered that the blue reaction that is produced by citrinin and ferric chloride diluted in ethyl chloride could be used to measure citrinin of low concentration. Chemically, Wang Yu and group utilized platinum oxide as a catalyst after which hydrogen was introduced to produce dihydrocitrinin, determined what was supposed to have been resorcinol B as resorcinol A and defined the externally racemized compounds of its crystal bodies. Using levo-resorcinol or resorcinol formate as the raw materials that undergo action by hydrochloride, formaldehyde or chloromethyl ether, stannic acid, they were able to introduce toward the carbon nucleus a side carbon chain that also became a ring to produce decarboxyl- dihydrocitrinin or dihydrocitrinin respectively. Then these dihydro compounds produced decarboxy citrinin and citrinin respectively after oxidation by ferric chloride. At the same time, they proved that dextro-citrinin could be obtained the same way through using dextro-resorcinol as the raw material. They are the mirrored crystal bodies of citrinin as occur in Nature, and their antibacterial effect toward certain bacteria is the same as natural citrinin.

In the field of antibiotics certification, the Antibiotics Section of the Central Bureau for Certification of Biological Products and various local antibiotics certification agencies that have been in existence since 1952 were responsible for the certification of antibiotics, by making the rules and regulations and preparing standard antibiotics for certification purposes. At the same time they made certain improvements on certification techniques and created new methods to raise the quality of such certification work. Due to the fact that there was no foundation for antibiotics production in the old China, the need of the people requiring antibiotics depended on foreign imports. Therefore, during the first few years that research into antibiotics developed, there was an urgent need to develop the production of known antibiotics on a large scale. For this reason, it was necessary for work engaged in the search for new antibiotics to go at a slower pace. At the Institute of Pharmacology of the Chinese Academy of Sciences, the Fukien Normal College, and the Fungi Laboratory of the Central Institute of Hygiene (formerly the Chinese Institute of Medical Science), only small effort was diverted to this type of work. In 1956, Wang Yao-tseng of the Fukien Normal College discovered the actinomycin C producing spore strain and extracted from it an antibiotic that underwent preliminary clinical trial. Tsai Jun-sheng et. al. of the Institute of Pharmacology of the Chinese Academy of Sciences conducted a more comprehensive analysis of the antagonistic soil actinomycetes that were found in different areas of Kiangsu and Chekiang provinces. In 1957, they found a new actinomycin producing (actinomycin K) strain, from which actinomycin K was extracted and used in the experimental treatment of cancer in mice with good results.

This is an antibiotic with some promise for use against cancer, and it is undergoing clinical trial at the present. Beginning in 1956, in accordance with long range scientific planning, research on new antibiotics by the Department of Antibiotics of the Chinese Academy of Medical Sciences and the Institute of Pharmacology of the Chinese Academy of Sciences was intensified under the leadership of Soviet and Polish specialists. In 1957, this department began the screening and selecting new antiviral, antitumor, and antibacterial antibiotics with particular attention on antitumor antibiotics. In 1958, when the department expanded into institute proportions, research on developing screening and selection methods for new antibiotics was initiated, and some new techniques have been adopted to raise the volume and quality of screen-selection. In the field of new antibiotics research close liaison has been maintained with the Soviet Union's Institute of Antibiotics Research through mutual exchange of research results, comparison of screen-selection methods which have been of great assistance to research at the Institute of Antibiotics.

Research on new antibiotics has stimulated the study of actinomycetes classification and bionomics. The Institute of Microbiology and the Institute of Pharmacology of the Chinese Academy of Sciences, the Institute of Antibiotics of the Academy of Medical Sciences have basically mastered methods for the standardization and certification of actinomycetes. They have standardized many known strains and described some new strains. This year they intend to establish the first standardized batch of some 500 spore strains as a salute to the nation's tenth anniversary, and they are also in the process of preparing material for a new classification system. In the field of actinomycetes bionomics, much work has also been done and much meaningful material has been accumulated. Through a gradual understanding of these microbes, especially the bionomic distribution of antagonistic actinomycetes in certain localities throughout China, much help toward the screening and selection of antagonistic bacteria is obtained.

In the field of broadened antibiotics application, research on it was begun in 1957. The Department of Nutrition of the Chinese Academy of Medical Sciences and the Chinese Institute of Agricultural Sciences cooperated together to prove the effect of aureomycin in stimulating animal growth. In cooperation with related units and farms, they are testing the growth stimulating effect of antibiotics on chickens at present. In order to push the manufacture of antibiotics for fowl use down to the village level, the Institute of Antibiotics of the Chinese Academy of Medical Sciences conducted research on a solid culture medium made of wheat gluten to culture the *Streptomyces rimosus* for terramycin to be used by fowl and the result was a product containing 4,000 micrograms of terramycin per gram of dry weight. Production facilities and processing techniques for the manufacture of this product are quite simple and suitable for use in a village environment. This method has been introduced to the people's communes for general use.

In the search for antibiotics to fight plant diseases, the united efforts of the Chinese Academy of Sciences and the Chinese Academy of Medical Sciences in this field began at the same time that the search for antibiotics for medical use was initiated.

Erythromycin that has a stimulating effect on plant growth has been manufactured experimentally by the Department of Plant Protection of the Peking Agricultural College and the Institute of Antibiotics of the Chinese Academy of Medical Sciences. Some of the manufactured product has been used by the Department of Plant Protection on many types of plants where an obvious growth stimulating effect is noticed.

Common antibiotics internationally used total more than 20 types. Of these, penicillin, syntomycin, streptomycin, aureomycin, neomycin, tetracycline, erythromycin, terramycin, etc., China has been able to produce. In a new situation under plans of a great leap forward, the workers in antibiotics endeavor to study and produce many kinds of commonly used antibiotics during the next two years to meet clinical needs and attain the internationally advanced level of quality. At the same time, new antibiotics that are anti-tumor, antiviral, and antibacterial need also be found. In the field of antibiotics research, besides assurance to see that the above mentioned tasks will be completed, theoretical research must also be carried out to point the way for production and therapeutics. Examples are research on the physiology and biochemistry of antagonistic bacteria, the biosynthesis of antibiotics, control of the effect of antibiotics, etc. In the field of antibiotics chemistry, penetrating study of extraction methods, work foundation, and the chemical structure and the various forms and dosages of antibiotics must further be studied to reduce toxicity and raise therapeutic effectiveness. Spore strains with a high production capacity must be selected. It is most important that the pattern governing the mutation of antagonistic bacteria be grasped. At the same time that the search for new antibiotics goes on, classification and the bionomics of antagonistic bacteria and improvement on techniques must be studied. Theories of the Party must be put into effect and the direction of mutual cooperation must be practiced.

Antibiotics research in China and the development of production has been very rapid. The fact that such achievements have been possible is due to the correct leadership of the Party and the expression of communism's spirit of cooperation after the people's thinking has been liberated and superstitions has been broken down. In 1958, we must double our efforts on the foundation of the great leap forward, so that even greater contributions may be seen in the field of antibiotics.

#### IV. ACHIEVEMENTS OF THE PHARMACOLOGICAL SOCIETY OF CHINA

[Following is a translation of an unsigned article in the Chinese-language periodical Yao-hsueh T'ung-pao (Pharmacology Bulletin), Peiping, Vol. VII, No. 10, October 1959, pages 489-491.]

##### I

The Pharmacological Society of China has been established for almost 50 years. However, before the Liberation, due to the semi-feudal and semi-colonial society that was then existent and the destructive attitude of the governments of the Pei-yang warlords and the reactionary Kuomintang, the work of this society was never able to progress and remained in a stagnant state.

After the Liberation, there was a basic change in the complexion of pharmacology just as there were changes in other fields. Due to the astute leadership of the Chinese Communist Party and our great leader Chairman Mao and the efforts of pharmacological workers throughout China, more than 80% of the medicines and pharmaceuticals used by the nation now are self-supplied and the picture of dependence on foreign supplies for pharmaceutical processing in the past is basically changed. Pharmaceuticals such as antibiotics, sulfonamides, vitamins, hormones, etc. which were considered impossible to tackle before the Liberation are being manufactured on a scale closely approaching self-sufficiency. The production of traditional Chinese drugs has also seen a one fold increase since the Liberation. Pharmacological research has also seen leaping forward development. In the search for new and effective drugs to overcome serious diseases, the heritage of traditional Chinese medicine continues to grow and changes in the course of drug production have met with great results. A pharmaceutical products supply network on a national scale has been completed and the supply of medicines has penetrated the level of the industrial areas and villages. Basically, the idea of "where there are people there exist medical care and medicines." More than 30 drug inspection and certification structures have been set up. Pharmaceutical plants, medicines trading agencies, and hospital pharmacies have also established individual inspection units to supervise each phase pertaining to production, supply and dispensing of pharmaceuticals to definitely assure the safety and effectiveness of the drugs used by the people. Such accomplishments are outstanding. Under the positive leadership and concern of the Party, and the active efforts of its many members, the Pharmacological Society of China has seen great development with its definite accomplishments during the past ten years.

## II

According to the direction given the work of the Society by the Party and the government the chief task of the Pharmacological Society is to mobilize pharmaceutical workers throughout China to cooperate, to closely coordinate production and health activities, initiate scientific activities to exchange technical ideas, to carry out the technological and cultural revolution and to be an efficient tool and assistant for the establishment of socialism and communism. In these ten years, the scientific activities of the Society have revolved around this central task.

Shortly after the Liberation, pharmacological workers throughout China hurriedly established local units of a Pharmacological Society nature under the leadership of the local Party and government units. Scientific activities in many forms, as lectures, seminars, science panels, training courses etc. were conducted. Some localities even published their own periodicals. Examples were Pei Hua Yao Hsin (North China Drug News) published in Peking, Yao-hsueh Hsueh-hsi (Practice of Pharmacology) published in Tsinan, Nanking Yao Hsin (Nanking Drug News) published in Nanking. These scientific activities and periodical publications had a definite effect in giving the scientific activities of pharmacology in the new China impetus and raising the occupational level of the pharmacological workers. In November 1952, the First National Conference of the Pharmacological Society of China was held in Peking. Besides the reading of papers and scientific lectures and discussions, problems related to education in pharmacology, reorganization of research into traditional Chinese drugs, pharmaceuticals production, etc. were also discussed and studied with recommendations sent to the related government agencies. In 1953, when the 1953 edition of the Pharmacopeia Sinica was published, the Society stimulated its local units to a great discussion of the Pharmacopeia which resulted in more than 2000 constructive ideas pertaining to its contents coming in. Since 1953, the local branch units of the Society in Wuhan, Tientsin, Hangchow, Chungking, Chengtu and other places organized the local pharmacy workers to study and improve on the work done at the pharmacy level with definite results. For this, the local health agencies paid them much attention. On this foundation, the local branch units of the Society in these places edited their own local editions of a United Formulary which were well received by comrades in the medical and pharmacological fields. In order to assist the local health administration agencies in their supervision of product quality in the pharmaceutical plants, the Shanghai branch of the Society unified manufacturing requirements and set up a conference to edit Standards for Pharmaceuticals which stimulated a rise in the standard of production quality in pharmaceuticals. The Tientsin branch of the Society organized more than 50 pharmaceutical plant members to exchange ideas on their pharmaceuticals inspection and certification experiences, and thereby raise pharmaceuticals certification techniques which showed in an obvious rise in product quality after that. Branch units of the Society at places such as Peking, Wuhan, etc. organized short inspection training courses to attract the participation of their members. The Chungking branch unit edited a concise inspection handbook which was used as work reference.

At some branch units, the members were organized to conduct special problems panel discussions to help production and health agencies to solve certain problems related to production techniques or organize field trips for members to see pharmaceuticals manufacture in operation and express their views on production or its techniques. Most branch units of the Society assisted their local administrative agencies by conducting training classes, night courses etc. to raise the level of occupational knowledge for pharmacological workers and cadres on the job and to actively train more technical workers for the field of pharmacology. After 1955, besides carrying out scientific activities of a more general nature, branch units of the Society everywhere also paid much attention to meetings organized to report on and discuss scientific papers in such a way that it was possible for one specific topic to be discussed thoroughly in the spirit of "a hundred flowers." Under slogans of "March against Science!" and "Catch up with the International Level of Advanced Science!" the great numbers of Society members were further inspired to put even more effort into scientific research. Following this, the number of scientific papers coming from the branch units of the Society everywhere continued to increase and improve in quality. In 1956 when the Second National Conference of the Pharmacological Society of China was held, more than 150 papers were received. Other local branch units of the Society such as those in Shanghai, Nanking, Canton, Hangchow, Peking also edited collections of scientific papers. The National Conference for the Discussion of Scientific Papers (which was originally called for in 1957) sponsored by the Society also received more than 300 papers of high quality content and most of the titles on these papers coordinated the reality of production with the reality of health measures (such as research on the drugs used for the prevention of serious illnesses, research on traditional Chinese drugs, etc.).

In order to coordinate the development of research in pharmacology with the exchange of advanced technological experiences on a large scale, the Society began in 1953 to publish Yao-hsueh Hsueh-pao (Pharmacology Journal), followed by Yao-hsueh T'ung-pao (Pharmacology Bulletin), Chung-yao T'ung-pao (Chinese Traditional Drugs Bulletin), Yao-hsueh Wen-chai (Selected Papers on Pharmacology), a total of four periodicals. The publication of Yao-hsueh T'ung-pao has now reached its seventh volume, and 226 papers have been published in it during this time. Besides subscriptions to it from readers throughout China, this journal also carries exchange subscriptions with pharmacology journals in many countries to aid exchanges of pharmacology on an international level. Since 1955, the total number of copies of Yao-hsueh T'ung Pao printed has exceeded 20,000 copies. Due to the fact that the contents of these journals constantly complement health policies of the Party, coordinate occupational reality, carry timely exchanges of technical experiences, and direct discussion toward certain problems in the spirit of "a hundred flowers," they have a stimulating effect on work in pharmacology. Since it first began publishing in 1955, the contents of Chung-yao T'ung-pao have emphasized the exchange of Chinese traditional drug techniques, helping those working on western drugs to learn the traditional Chinese drugs method. More than 10,000 copies

are printed for each issue and this journal has received the broad attention of western drug workers and traditional Chinese drug workers throughout the nation. In April 1959, this journal was combined with Yao-hsueh T'ung-pao in order to stimulate the close cooperation of workers in western drugs and those in traditional Chinese drugs and make it easy for them to learn from each other. Yao-hsueh Wen-chai was first published in 1958, but it is now edited by the Shanghai branch of the Society and carries timely reports on conditions of pharmacological research in China and abroad for the reference of the scientific worker in pharmacology.

During the national great leap forward in 1958, the beginning of the technological revolution opened up a new situation for scientific activities of pharmacology in China. Under the stimulation of such a situation, the two bulletins sponsored by the Society has carried and popularized the accomplishments of technological reforms and the results of scientific research in a timely manner reflecting the leap forward complexion of the pharmacological profession throughout China. Abundant production experiences of Chinese traditional drugs introduced in Chung-yao T'ung-pao and the two books it assisted the Bureau of Drug Administration of the Ministry of Health to write, where experiences in the abundant production of Chinese drugs and experiences on transforming wild plants into domesticated ones were introduced, had a definite effect on stimulating the growth and production of Chinese drugs. Yao-hsueh T'ung-pao opened up a special column in the journal to introduce on a large scale, accomplishments of technological reforms on the people's level. Take, for instance, the automatic individual medicine wrapper that was a successful invention of pharmacist Chiang Chung-hsien at the 262nd Hospital of the Liberation Army. This was immediately introduced in Yao-hsueh T'ung-pao. At the same time branch units of the Society at places like Peking, Tientsin, initiated scientific activities pertaining to technological reforms in conjunction with Comrade Chiang's invention. Other branch units also did many things while engaged in activities initiating technological reforms. Some branch units organized their members to assist production agencies to produce exhibits to promote technological reform, conduct experience exchange groups, edit related pamphlets, etc.

### III

In order to realize the Party's policy on Chinese traditional drugs, and to continue and develop the heritage of traditional Chinese medicine, the Society formed a Committee for Traditional Chinese Drugs Reorganization (which was later changed to the Committee for Traditional Chinese Drug Research) in 1953 to undertake research and edit reference material appraising commonly used traditional Chinese drugs under the direction of the Ministry of Health. In carrying out this undertaking, local branch units of the Society everywhere were asked to organize local workers connected with pharmacology to participate. Toward the end of 1956, more than 100 items of reference material appraising commonly used traditional Chinese drugs completed by the branch units everywhere were received with 1114 samples of medicinal plants and 1048 samples of crude drugs. The Committee has reorganized this reference material appraising Chinese drugs,

and intend to publish them in separate collections, for reference by workers in related fields. Its first collection was published in 1958. However, due to the fact that certain workers in the field of pharmacology in the past looked down on the Chinese drug practitioners and traditional Chinese drugs with the typical capitalist attitude of class consciousness, while doubting their inclusion in the field of science, the one tracked approach toward traditional Chinese drugs with the viewpoints and methods of western medicine in those who had never learned anything about traditional Chinese medicine, and other incidences where workers in traditional Chinese medicine have been discriminated against and denied membership into the Society, development of traditional Chinese medicine suffered a definite setback. After a thorough understanding of the Party's policy toward traditional Chinese drugs, and the empty argument against traditional medicine practitioners and traditional Chinese drugs on nationalistic grounds had been rectified, a proper attitude toward the cultural heritage of traditional Chinese medicine was developed, cooperation between workers in the fields of western and traditional Chinese drugs was intensified, and a movement to learn about traditional Chinese drugs was underway among the workers. The Society and its branch units everywhere were conducting scientific activities in many aspects regularly. Examples were panel discussion on traditional Chinese drugs, exhibits of these drugs, panel discussions on specifications and standards for these drugs, survey of drug sources, editing or helping professional agencies to edit books on traditional Chinese medicine of the handbook type (such as a Compilation of Drug Materials co-edited by the Shanghai branch of the Society and the Shanghai Drug Co. Volume I of two volumes has been published and Vol. II is pending), conduct of research activities on the improvement and conversion of the forms of drug preparations, etc. In this way, great impetus was provided the movement to learn more about traditional Chinese medicine and drugs. The two bulletins also conveyed knowledge on traditional Chinese drugs and introduced their other aspects, such as methods and approach, to the readers.

#### IV

Strengthening international scientific exchange is another purpose of the Society that has had much effort put into it. During the past few years, pharmacologists from brother nations such as the Soviet Union, Hungary, Czechoslovakia, Poland, Roumania, the German Socialist Republic, the Korean People's Socialist Republic and other nations such as Japan, Egypt, etc., who have come to China to visit or work have been received by the Society. Some of them have given lectures; others have conducted panel discussions. When abroad, responsible officers of the Society have also made contact with pharmacologists of other countries and exchanged scientific ideas and experiences with them. Besides this, a journals exchange system was also established between the Society and many brother nations.

Pharmacologists in China have always paid much attention to learning from the great accomplishments and advanced techniques of pharmacology in our brother nations such as the Soviet Union, etc. During the past ten years, practically all the specialists coming from the Soviet Union and

other brother nations to China have met some of the Chinese workers in pharmacology. Some of these workers have even made reports, a fact which shows a favorable climate for learning from the advanced experiences of the Soviet Union. Pharmacology comrades who have returned from visits or studies in the Soviet Union also reported on their experiences on a local level, thereby giving China's pharmacological profession a greater understanding of the Soviet Union's advanced pharmacology. In order to assist pharmacology workers everywhere to study Soviet experiences better, branch units of the Society at places such as Tientsin, Peking, Canton, etc., conducted quick Russian courses while the Society itself, published in conjunction with the International Bookstore, study material such as the Pharmacopeia U.S.S.R., reported on the new accomplishments of Soviet pharmacology in various fields and the advanced theories and experiences of Soviet medicine regularly in Yao-hsueh T'ung-pao and also edited a book called An Introduction to Pharmacology in the U.S.S.R. for publication.

After studying the advanced experiences of the Soviet Union, many members coordinated their learning with reality to improve and raise the level of their work. For instance, some members from places such as Peking, Shanghai, Tientsin, Nanking, Chengtu, Nanchang, Tsinan, Tsingtao, Changchun, Sian, Fuchow, etc., used a quick inspection method to check on the quality of pharmaceuticals in the pharmacy and the semi-finished product in the pharmaceutical plant, which has resulted in raising the quality of pharmaceuticals. Having been exposed to the advanced experiences of the Soviet Union, many members have set up systems of pharmacy inspection and measurement control within their own pharmacies to improve their work. Members who work in pharmaceutical plants in places such as Shanghai, Changsha, Hangchow, Mukden, Tientsin, Chungking, etc., also made many improvements and raised the quality of work with regard to pharmaceutical manufacturing techniques as the result of serious study of Soviet experiences.

V

During the last ten years, organization of the Society continues to develop on a solid basis. By the third quarter of 1958, 28 branches and units of the Society were counted throughout China, with a total count of 3,020 members which included 153 working with traditional Chinese drugs. (New members acquired with expansion of the Society following organization of the National Association for the Advancement of Science have not been counted.) Due to fact that during the early period after the Liberation, organization expanded so rapidly, there was no serious effort toward reorganization. Therefore, beginning in 1953, a complete reorganization was carried out so the Society is on an even more solid base. Party leadership within the Society is gradually intensified, and activities of the Society are gradually being steered on the right course. These are factors contributing to the smooth development of the Society's activities.

As a professional society under the socialist system, the Society has a great responsibility toward the unity, education and reform of its members. During these ten years, due to the assistance given Party education through the Society's periodicals, news letters, reports, and conferences, the ideological thinking of the members underwent great transformation.

Particularly after several ideological movements, ideological training was obtained during the actual struggles. Therefore, unproletarian attitudes such as capitalist individualism, indifference toward politics, separating theory from reality, belittlement of the masses' wisdom and creativity, etc., which were inherited from the old society were all seen in their proper light and changed. However, somewhat more outstanding was the great victory won by the Anti-rightist Movement that developed in 1957 on a nationwide scale. This movement was a moving, real and penetrating experience in socialistic education for many members of the Pharmacological Society of China and even workers in pharmacology throughout the nation. Before the Anti-rightist Movement, the thinking of a comparable section of workers in the drug industry showed a certain degree of confusion when they felt health agencies were emphasizing medicine, but overlooking medicines; that outsiders were not able to lead insiders; that pharmacy practice was not what it used to be, etc. After the Anti-rightist Movement and the Rectification Movement and particularly after the stupid anti-Party and anti-socialist words and deeds of rightist elements were firmly exposed and criticized by the Society and its branch units everywhere, Party and political leadership was truly implanted in the various activities of the Society. At the same time, the level of ideological consciousness on the part of workers in pharmacology everywhere was greatly raised, the workers were basically able to determine right from wrong, the determination to follow the Party on the course of socialism was set, the attitude of using their technical ability for political service and directed toward production and reality was implanted in their actual work, and mistaken tendencies such as separating techniques from politics and research from reality were changed. Without doubt, the victory of this movement has exercised a great and stimulating effect on development of the Society's activities for now and the future and the ideological reform of pharmacology workers throughout China.

## VI

While the activities of the Pharmacological Society of China have resulted in the achievements just described under the correct leadership of the Party and government, they have yet to meet the needs of the people. All of our pharmacology workers are determined to support calling of the 8th Session of the 8th Central Plenary Conference and their resolution to initiate an increased production and waste cutting movement. We are determined to respond to the call of the Party from our pharmacological posts to continue fighting rightist elements, and with great enthusiasm, to go forward under the red flag of Party construction and socialistic direction. Activities for now and the future must be under the light of socialism, and Party policy must be followed on health matters. Pharmacological workers everywhere must be united and mobilized; production and health activities must be coordinated, and scientific activities must be initiated. Activities on political ideology must continue to be intensified to increase the ideological consciousness of the Society's members. Workers on western and traditional Chinese drugs, old and young workers must cooperate with their

goals directed at production and reality and continue to raise the level of their techniques based on principles of popularization, increased coordination, and coordination of western and traditional Chinese drugs. This way, the assistance given the health agencies is able to be exercised fully in service to the people's health, to China's socialistic construction, and in efforts to gain even more glorious achievements for the field of pharmacology during the next ten years.

## V. CHINA'S ACHIEVEMENTS IN THE FIELD OF PHARMACY

Following is a translation of an article by Ho Mao-chih and Wang Hung-ch'en in the Chinese-language periodical Yao-hsueh T'ung-pao (Pharmacology Bulletin), Peiping, Vol. VII, No. 10, October 1959, pages 492-496.

Before the Liberation, due to exploitation by the imperialists and the reactionary government's neglect of the people's health, production of pharmaceutical preparations was extremely backward. Not only was the technological "know how" very poor, production facilities were also very crude. At that time, due to dumping of pharmaceutical preparations by foreign countries on China in great volume, and the destructive effect of the reactionary government on the drug industry, pharmaceutical production in the old China simply did not have a chance to develop. Pharmaceutical preparations that were produced by a few pharmaceutical plants at that time were mostly crude and substandard, and the market was just flooded by inferior drug preparations and imported drugs some of which were harmful to the people's health. As for pharmaceutical research to raise the quality of pharmaceutical preparations, that was simply out of the question.

After the Liberation, the Party and government showed great concern for the people's health and put great effort into the development of a pharmaceutical preparations industry. The result has been a continual growth in pharmaceutical production with glorious achievements. The production of various kinds of pharmaceutical preparations at present, whether from standpoint of quantity or quality, has shown great strides. Pharmaceutical preparations that were unable to be produced in the past are now possible; techniques of the past that were substandard are now improved upon and made better. Therefore, there is no need for pharmaceuticals to be imported, as China is basically self sufficient now. Furthermore, there are some pharmaceutical preparations, especially those made from Chinese traditional drugs, that are sold on the foreign market where they are welcomed by the overseas Chinese and the local populace. Besides the manufacture of synthetic organic drugs and antibiotics, the manufacture of pharmaceutical preparations from Chinese traditional drugs that the great mass of people favor should also receive proper attention for its development. In recent years, especially after the great leap forward last year, pharmaceutical plants and drug pharmacies underwent reform of techniques on a large scale to obtain outstanding results after thinking had been liberated and superstitions had been broken down. In the field of research, the pharmaceutical plants, drug pharmacies, schools of pharmacy and other related units are all putting much effort into it and issue bulletins on the results of new research regularly. It can be stated quite positively that the production of pharmaceutical preparations and their research are making great progress in the new China.

#### A. Research on Pharmaceutical Preparations

Research on pharmaceutical preparations in the past has been on a small scale. During the last few years, due to outstanding developments in the field of pharmacology, research on pharmacy has also developed accordingly. Within the Research Institute of the Drug Industry under the Ministry of Industrial Chemistry is a Pharmaceutical Preparations Research Laboratory. In the various schools of pharmacy, research on pharmaceutical preparations is also carried out. Results of research in various fields will now be introduced in the following paragraphs.

Concerning antibiotics preparations, research<sup>(1-4)</sup> has been conducted on problems pertaining to aureomycin and tetracycline in parenteral solution and eyedrops form. In research on parenteral solutions of aureomycin, tests were made to compare the solubility of aureomycin in solutions of magnesium chloride, vitamin C, and sodium glycine. Results show that its solubility in 0.9% sodium glycine attained a figure of 10mg/ml, and it also showed a buffer action which made it suitable for intravenous use. This parenteral solution was not too stable. After two hours at 2°C, there was a loss of 14.95%. After half an hour at 17°C, the disintegration was 13.29%, so the solution had to be made just before using as it could not be stored. In the preparation of tetracycline, the purification method had been tried and studies on its stability were also made. At present, certain factors governing the preparation of its parenteral solution and eyedrops are known and a tetracycline solution-tablet for ophthalmological use has been prepared. This solution-tablet may be dissolved in distilled water at the time of using. The pH value of the solution ranges between 7.5 and 7.8, and it is also isotonic. Improvements have been made to increase its stability. After two days at 30° to 36°C, disintegration is about 10%; after eight days at 20° to 25°C, disintegration is 10.56; and after a month in a refrigerator, there is hardly any disintegration. The addition of sodium bisulfite and propyl-pyrogallol acid as antioxidants into the ophthalmic solution will raise its stability. The lower pH value, the better the stability. However, irritability to the eyeball must be considered, so a pH value of 6.4 is more suitable.

The solubility of chloromycetin in water is very small, so that the preparation of an intravenous injection of small dosage has been an urgent problem requiring solution. Research on this is successful now<sup>(5)</sup>. Addition of dextrose to chloromycetin which is then dissolved in distilled water to be used for injection will result in a parenteral preparation. This preparation will show its bactericidal effect in 30 minutes at 100°C, quite suited for pediatric use.

Under the Party's banner to eliminate bilharziasis, the medical and pharmacological professions have done a great amount of work on drugs and medicines to fight bilharziasis. From these, the use of antimony compounds has shown very good results. Due to possible irritations caused by antimony compounds on the gastrointestinal tract to produce unfavorable reactions, research on the form of oral antimony compounds has received much attention which has resulted in a certain amount of success.

The successful preparation of an antimony potassium tartrate enteric capsule<sup>(6-7)</sup> has made it possible for the antimony compound capsule to pass through the stomach intact until arrival in the intestines where it disintegrates to release the medicinal effect. The enteric capsule is a glutel capsule made from gelatin that has been treated with formaldehyde. Though this capsule film does not disintegrate in the stomach, the antimony compound can still penetrate this film to release its medicinal effect which still irritates the stomach. Therefore, after treatment by formaldehyde, the glutel capsule should be coated with a layer of stearic acid or cetaceum to prevent the above mentioned drawback. Tests have proven this type of gelatin capsule does not irritate the stomach and its absorption in the intestines is quite good making it possible for the blood antimony content to attain required levels.

With research on the enteric soluble coating, the problem of bonding the antimony compounds<sup>(8)</sup> also made definite progress. It was found that when shellac only is used for the coating, the thickness of the coating layer is hard to control so that stability of the drug's therapeutic effect is hard to assure. Using an alcohol solution of mixed shellac and cetanol (10% of each) as the coating shows the best results. Generally, the coatings were maintained in artificial gastric juice for four hours without change, while complete disintegration takes place in artificial intestinal juices in 20 - 30 minutes. Experiments in vivo prove that the coatings can survive 1 - 3 1/2 hours inside the stomach without disintegration, but once inside the intestines, disintegration begins within 1 1/2 hours to 4 hours after, and disintegration is usually completed after 6 hours. It was also found that a mixture of shellac and castor oil also made an effective coating and an enteric coating made of opthalic acid cellulose acetate showed strong resistance to gastric juices<sup>but</sup> disintegration after 15 minutes in intestinal juices.

While it is possible to avoid and remove nausea and irritation to the stomach with enteric capsules and pills of antimony compounds, but due to the concentration of the drug in the intestines, abdominal pain, diarrhea and other side effects often take place. Therefore recent research<sup>(9)</sup> has continued from the foundation of the enteric coated pill preparation and expects to slow down disintegration of the pill preparation and release of hetmedicinal substance by adding an appropriate amount of high quality fatty acid during the process of granules preparation. Present experiments on animals have obtained preliminary results.

Other methods to counteract the unfavorable reactions of antimony compounds and preparations are in the process of research. Examples are preparation of potassium antimony tartrate in suppository form<sup>(10)</sup>, or preparing it in form of antimony ammonium salts of glucose and sucrose, etc.<sup>(11)</sup>. These preparations have been tried on animals and shown very good absorption. However, their actual effectiveness in clinical use require further research. Research on antimony potassium tartrate tablets prepared by the drop pill method<sup>(12)</sup> is a preliminary success.

Research on extract preparations has concentrated on production techniques and the processing of new extract preparations. For example, the problem of tincture precipitation in China on the industrial production level has been quite serious, but after some research<sup>(13)</sup> certain patterns have evolved. The liquid extract and tincture of belladonna for instance, are extracted with a chloroform solution containing tartaric acid as the solvent. The concentrate is then precipitated with alcohol or extracted with 80% alcohol. After concentrate processing under diminishing pressure, water is used to precipitate the useless matter, and a product prepared in this manner shows very little precipitation during storage and the color is uniform. Use of the continuous circulation percolation method to prepare liquid extract of gentian results in a clear product that shows a drop in precipitation after several months storage. But the same extracts prepared from the methods prescribed in the Pharmacopeia show a great amount of precipitation after several months of storage.

In the field of new extract preparation (new galenical preparation), China has paid attention to this form in recent years and utilized its method. Injections are now prepared from native grown ergot<sup>(14)</sup> and chemical analysis shows them to contain water soluble ergotmetrine and non water soluble alkaloids. The injection preparation is a colorless clear solution which proves after pharmacological tests its obvious effect on the uterine contractions of rabbits and cats. It does not show any obvious effect on blood pressure and respiration and is being tried clinically at present. The extraction of glucosides of *Strophanthus divaricatus* (Lour) Hooket Arn and clinical observations on their use are preliminarily successful<sup>(15)</sup>. The results show that the effectiveness value of the total glucosides is comparable to that of imported strophanthin - k, the effectiveness value of isolated glucoside that shows a mild lipid affinity is 150% that of strophanthin - k<sup>(16)</sup>. Injection solutions are prepared from these extracts now and pharmacological and clinical tests are being carried out on them. Parenteral solutions of *Bupleurum falcatum* L. and *Bupleurum sachalinense* are prepared from their extracts which are then distilled, and these solutions are effective as antipyretics.

The method of preparation by "squeezing juice from grass" has been recorded in many taxonomy annals of Chinese history. However, learning from the advanced experience of the Soviet Union in recent years, China has developed the preparation method of pressure squeezing juice from fresh medicinal plants. An example is seen in squeezing the juice from *Capsella bursa-pastoris* Moench. 30% warm alcohol is used to treat the residue after which it is pressed, squeezed and filtered to become a juice preparation in proportions of 1 : 1 alcohol and residue. Each dose of 10 ml may take the place of tincture of ergot in obstetrical use<sup>(18)</sup>. Research<sup>(19)</sup> on the liquid extract preparation method used on plants from the Solanaceae family proves the many advantages of press-squeezing the fresh belladonna leaves to obtain the liquid extract. For instance, convenience to the concentration process, saving on alcohol waste, cutting down evaporation of the drug in transport, etc.

On the method of drug roasting practiced with Chinese traditional drugs, there has also been some research. Research results on obtaining an extract from roasted betelnut<sup>(20)</sup> which is used as a vermifuge against tapeworm show that regardless of the degree of pulverization of the drug, by using the roasting method, only a little more than 40% of the alkaloids is extracted with a 53% loss. The time allowed for roasting is best set at 30 minutes, as a longer roasting period does not raise the extraction rate. The effectiveness of alkaloids obtained by the extraction method is not higher than that obtained with the roasting method. It was also discovered that the extract efficiency of the extract method shows an irregular drop due to an increase in the fineness of the powder.

In the search for cocoa butter substitutes, some fairly satisfactory matter such as the esters of *Sapium sebiferum* Roxb. and *Conioselinum univittatum*, Turaz which are used as the base for suppositories. The ester of *Sapium sebiferum* is obtained from the oils contained in the skin of the fruit, is a white solid at room temperature, has a melting point which ranges from 38° to 42° C, while its softening point is found between 31.5° and 34° C. After some research<sup>(21)</sup> it is felt that the ester of *Sapium sebiferum* can be used as a cocoa butter substitute. Melting it at 100°C does not affect its solidification, and this is one feature not seen with cocoa butter. When ester of *Sapium sebiferum* is prescribed with tannic acid, lead acetate etc. the change in melting point is not obvious, but when prescribed with fat-soluble drugs such as phenol, chloral hydrate, etc., the melting point drops. Testing it with the Gross test tube colorimetric method, its drug releasing power is not as good as that of cocoa butter. *Lindera communis* Hemsley is a tree of the Lauraceae family grown in Yunnan province. Contained in its fruit pit is a kind of solidified fat that is white, with a melting point of 34° C, saponification value at 276.4, acid value 0.294, iodine value 1.206. After some research, it was tried as a base for suppositories. Hemorrhoid suppositories and gentian violet suppositories made from it proved to be effective, and without any irritation effects.

Utilizing the gum content of certain traditional Chinese drugs to substitute for gum arabic or tragacanth gum is also quite meaningful. At present, the gums of two drugs have been determined suitable. One is salep gum<sup>(23)</sup> whose suspension ability toward barium sulfate is stronger than that of the same concentration tragacanth gum and gum arabic, whose dispersion ability toward mineral oil, fatty oils, and volatile oils is weaker than that of mucilage of gum arabic, though the viscosity of the dispersing agent is increased, its stability maintained and the amount used is 1 - 4 times less than gum arabic. The other is the gum of plantago seed which may be used either as an emulsion or suspension. Its dispersion ability toward mineral oil is the same as that of gum arabic, its dispersion ability toward fatty oils and volatile oils is weaker than gum arabic, but its suspension ability is greater than that of gum arabic and tragacanth gum, thereby making it a suspension that may be used for drugs such as sulfonamide drugs, phenacetin, etc.

Research on substitutes for almond water has discovered the usage of plum pits (25) and loquat pits (26) from trees grown in Szechwan province. They can be used as almond substitutes in the preparation of aromatic cough medicines. Blossoms of Magnolia Kobus, DC show effects of clearing the nasal passages, draining the sinuses, and relieving congestion. Preliminary tests at present have proved that the effective component in these blossoms is a volatile oil that has incorporated into preparations such as aromatic waters, emulsions, suspensions, etc. Trial of these preparations on all types of rhinitis show the emulsion to be the most effective.

In the field of injections preparation, various pharmaceutical plants throughout the nation have come out with many inventions and improvements. An example is research on sterilization conditions and methods (28) surrounding the preparation of injections. It states the importance of processing room conditions and raw materials on the sterility of the product. Among the three raw materials, thiamine hydrochloride, ascorbic acid and dextrose that are used, should dextrose containing bacteria and contaminated distilled water be used for the preparation of the injection solution, the presence of bacteria is very seldom detected after compounding and filtering. It states that suitable preparation and filtration can lower bacteria contamination tremendously or it is even possible to render the preparation completely bacteria free. As for the method to be used to sterilize the injection solution, it must be determined according to sterilization conditions in the processing room. Experiments have proven that dextrose subject to 100°C for 45 minutes, ascorbic acid to 100° for 15 or 20 minutes, thiamine hydrochloride to 100 for 20 or 30 minutes will be rendered sterile. However, when the solution is contaminated by bacteria spores with a stronger heat resistance, the bactericidal temperature and the time interval for this to be maintained must be increased.

Much importance has been given to research into the stability of various kinds of analgin injection. Injection solutions of analgene? contain aminopyrine derivatives that undergo chlorination easily and change color. Research (29) has proved that temperature and traces of metal ions such as  $Mn^{++}$ ,  $Cu^{++}$ ,  $Mg^{++}$ ,  $Fe^{++}$ ,  $Sn^{++++}$ ,  $Sn^{+++}$ ,  $Co^{++}$  etc. are factors hastening the oxidation of analgene injections solutions and causing them to turn color.  $p^H$  value also exerts a definite effect. Below  $p^H$  2, the solutions are comparatively stable. At  $p^H$  6 - 7, color change is most marked. Sulfites and thiourea may be used as stabilizers, though the introduction of  $CO_2$  gas is the best method. As for the problem of calcium gluconate sedimentation, experiments (30) have proved the sediment to be calcium oxalate, the presence of the sediment to be related to the purity of the raw materials used and the introduction of an accessory agent does not seem to affect this change. In the experiment, introduction of an oxidant causes calcium gluconate to undergo oxidation and become calcium oxalate, thereby producing a sediment. Whether or not the raw materials contain traces of oxidant matter whose description is not covered by certain pharmacopoeias is a problem worth further investigation. In the field of new injection preparations, an injection solution of natrii morrhuas (31) has been successfully prepared by the extraction of morrhuate from cod liver oil after which it is compounded according to prescription: 5 grams of

morrhuate, a suitable amount of caustic soda, 2 ml methyl alcohol, 0.31 gm of boric acid and distilled water to fill up to 100 ml.

Besides this, problems related to the application of water soluble ointment bases, surface activators, contact colloids in pharmacy are being studied.

#### B. Research into the Preparation of Pharmaceuticals in the Pharmacy and its Revolution in Techniques

Research into the preparation of pharmaceuticals in the pharmacy developed during the last few years. Where ophthalmic preparations are concerned, due to strict requirements and existing problems pertaining to the stability of the preparation and irritating effects on the eyeball, this type of preparation has received wide attention. A survey on bacteria contamination of 17 kinds of ophthalmic solutions used in 32 hospitals in Shanghai(32) shows the contamination rate to be as high as 37.1%, and contamination mostly by the *Bacillus pyocyaneus*. The chief channels of contamination are through too frequent opening and closing of the medicine bottle, contact of the medicine dropper with the patient's fingers and the eyes, etc. Among the solutions for ophthalmic use, contamination is most serious in those containing physiological saline. In order to prevent contamination of medicine which is harmful to the eyes, the effectiveness and application of various kinds of preservatives have been studied, and mercuric oxycyanide is recognized as a comparatively ideal preservative for ophthalmic solutions. Its test tube concentration of 1 : 15,000 applied on the cornea of rabbits show an obvious bacteriostatic effect, and its irritating effect on the eyeball is very weak.

Research into eyedrops prepared from the various sulfonamide drugs(33) states that the three kinds of eyedrops prepared from sodium sulfathiazole, sodium sulfadiazine, and sodium sulfacetimide yellow easily after a period of storage (especially the first two) and produce a sediment. Sodium sulfacetimide is more stable than the other two, and its alkalinity is lower. These three kinds of solutions need to be kept in light proof containers.

After preliminary research on physostigmine salicylate eyedrops(34), it is known that a 0.5% solution of physostigmine salicylate when kept in an ordinary glass bottle will change to a light red color within three days, to a red color in a week, and to a brownish red in three weeks time, due to the quality of the glass in the bottle. However, when kept in a container of hard durable glass, the color changes come on more slowly. Should an anti-oxidant such as sodium pyrosulfite (0.04%) and sodium bisulfite (0.1%) be added, the solution could be preserved for 30 days without changing color. At the same time, it was discovered that the effect of the solution on pupil contraction in rabbits was increased after the solution had changed color, though the maintenance time interval was slower. Research on the stability of atropine and factors affecting the hydrolysis of atropine(35) has also been conducted. Experiments prove that hydrolysis is more obvious when the pH value of the solution is 8.66 than when it is at 5.45 or 6.64. Temperature has a great effect on the hydrolysis of atropine.

Under conditions surrounding a pH value of 8.66, the time interval for atropine solution to reach a semi-hydrolyzed state at 5°C is 124,800 minutes; at 30°C is 5,021 minutes; at 100°C is 49.6 minutes. Therefore, atropine solutions should be stored at low temperatures.

The effectiveness value of gastric protein enzymes mixture is very unstable. Furthermore, there is no uniformity in the way it is prescribed in various localities. Research<sup>(36)</sup> in this aspect has come to some conclusions. It is recognized that the pH value greatly affects the preparation, and a pH value of 2 is the best. Growth of enzyme bacteria in the preparation also affects its effectiveness value. Adding a suitable amount of glycerine when the preparation is compounded will not only control bacterial growth, it will also aid solubility.

The injection solution of sodium phenobarbital is very unstable, so it is usually prepared in powder form and sealed in nitrogen under aseptic conditions for injection use. In other countries, glycol propylene, paraldehyde, etc., are used as solvents for phenobarbital injections. However, pharmacists in China have studied and experimented with alcohol and glycerine as a mixed solvent (6 : 4) to prepare a 10% sodium phenobarbital injection<sup>(37)</sup>. Sterilized with moist heat at 100°C for 30 minutes, its contents were found to meet requirements on inspection after eight months.

In research on garlic preparations<sup>(38)</sup>, it was discovered that *B. pyocyaneus* was the exception that does not show any sensitivity to garlic, though garlic has a bacteriostatic or bactericidal effect on other bacteria such as the staphylococcus aureus, the hemolytic streptococcus, *B. coli*, dysentery bacillus, the typhoid bacillus, etc. At present garlic is put up in many forms of preparation for clinical trial. Examples are garlic solutions, garlic ointments, tincture of garlic, garlic powder, garlic injections, etc.

In the last two years activity involving a revolution of techniques developed on the pharmacy level. Its chief activity concentrated on the following aspects: (1) Improved forms of preparation and better tasting medicines; (2) Invention and improvement of production tools; (3) Preparation of injection solutions that are painless and show a prolonged effect.

Work on improved forms of preparation and better tasting medicines: Placenta powder which is unpleasant to taste is hard to take, so it is made into pills<sup>(39)</sup> after washing and drying or made into fleshy looking mounds easier for the patient to take. Syntomycin tastes bitter so an equal volume of licorice powder is added to it and small balls are made according to a ball making method used with Chinese traditional drugs with each ball containing 10 milligrams of syntomycin which makes it convenient for pediatric use<sup>(40)</sup>. In other instances, addition of an appropriate amount of sperm whale, molasses, sugar, etc., to the medicine will result in a pleasant tasting syrup preparation to be used on children. Examples are sulfonamide candy, chloromycetin candy, decapryn lollipops, syrup suspension of aureomycin, effervescent powder of magnesium sulfate<sup>(41)</sup>,

etc. Chloral hydrate preparations irritate the stomach easily, so their prescription components have been suitably revised<sup>(42)</sup>. A starch paste is used as the medium to which a taste correcting agent such as syrup, tincture of orange, peppermint water, etc. is added and clinical applications prove that irritation suffered by the mucous membrane of the digestive tract is reduced. Suspensions of sulfonamide drugs now use a paste containing starch and cold sperm whale as the medium to which syrup and rose food coloring are added. Not only are the suspensions pleasant to taste, the suspension effectiveness is better, and the dosage is accurate<sup>(43)</sup>.

In the invention and improvement of dispensing tools used in the pharmacy, the manufacture of the automatic medicine scales and automatic medicine wrapper must first be mentioned. The automatic medicine scales is an improvisation of the ordinary dish scales except that medicines may be added on automatically until a balance is maintained and its efficiency is three times that of manual medicine scales. The automatic medicine wrapper<sup>(44)</sup> is made up of a motor section, a drive, volume regulator, pressure folder, sealer, printer, etc. It could wrap between 2,400 to 3,600 packets in an hour and their weight differential is within limits set down by the Ministry of Health. The machine is small in size which makes it very convenient to use. Besides this, many simple pieces of mechanical equipment such as a digital tablet counter, a specific amount pill scoop pertaining to pill counting, liquids transfer, filtering, etc.

In the preparation of painless injections with a prolonging effect, there are procaine injections with a prolonged anesthetic effect. Research in this field has come out with several results. One instance where 0.065 g of quinine hydrochloride and 2.5 ml of methyl alcohol are added to 100 ml of procaine hydrochloride, the anodyne effect of the preparation was extended<sup>(45)</sup>. Another instance where procaine was dissolved in a 2% or 3% oil solvent made from refined peanut oil to be used as an anodyne, such as effect was prolonged for a period as long as 20 days<sup>(46)</sup>. Besides, this, the addition of 2% methyl alcohol into a solution of thiamine hydrochloride will also result in a painless preparation<sup>(47)</sup>.

#### C. Research into the Preparation of Pharmaceuticals in the Pharmaceutical Plants and Their Revolution in Techniques

The production of pharmaceutical preparations at the level of the pharmaceutical plant has undergone great development during the last few years. Much experience has been obtained in the production of injections and tablet preparations which has shown very outstanding results. In 1956, the Bureau of Controls for the Drug Industry under the Ministry of Industrial Chemistry issued a pamphlet containing an exchange of experiences on techniques related to tablet preparations, injection preparations, ampule glass that was a summary of production techniques in these fields during the years after the Liberation. In the last two years rapid progress is further seen in research on pharmaceutical preparation and the revolution in techniques.

Due to much effort expended in research and experimental manufacture, many injection preparations that were impossible to make in the past are now possible. The experimental manufacture of protamine zinc insulin for injection<sup>(49)</sup>, dextro-rotary anhydride of saccharide<sup>(50)</sup>, Neo-Digalen<sup>(51)</sup>, norepinephrine injections<sup>(52)</sup>, Vitamin B<sub>12</sub> injections<sup>(53)</sup>, etc., has been successful and placed on a production level now. Certain parenteral solutions that are unstable are now prepared in powder form so that the quality of the pharmaceutical is assured. These powder preparations for injection include isoniazid powder, sodium sulfathiazole powder, sodium sulfadiazine powder<sup>(54)</sup> etc. Problems existent in injection preparations concern clarity and heat source mostly. Due to strict supervision of the preparation processes by the pharmaceutical plants, the problem of clarity in injection preparations has been fundamentally solved. Impurities such as fibers, glass grit etc., contained in the injection preparations are found in smaller amounts than the imported product<sup>(55)</sup>. Due to improvements in the plant equipment and hygienic factors, the heat source problem has also found preliminary solution, and there has been revision of the heat source inspection method used during the course of production<sup>(56)</sup>. The quality and quantity of injection preparations are closely related to the individual processing steps such as making up the solution, cleaning the ampules, filtering, packaging, sealing, sterilization, etc. In recent years, many revolutions of techniques have taken place toward individual processing steps involved in the preparation of injections in the various pharmaceutical plants. Take cleaning the ampules for instance. The pharmaceutical plants have come out with a semi-automatic ampule cleaning machine<sup>(57)</sup> which not only cuts down on manual labor by several workers, it has cleaned the ampules better and made improvements on the step of filtration<sup>(58)</sup>. Packaging the injections has also seen many revolutionary installations<sup>(60)</sup>. As for sealing the ampules, various pharmaceutical plants suggested many new methods such as the six flame sealing method to speed up the sealing process<sup>(61)</sup>. In the sterilization of injection preparations, a special method to sterilize procaine penicillin with ethylene oxide has been devised with good results. Parenteral solutions of vitamin C and vitamin B<sub>1</sub>, etc., are very unstable, so introduction of a slow acting gas into them to counteract oxidation will increase their stability<sup>(63)</sup>. Addition of E.D.T.A. into injection solutions of sodium salicylate and sodium iodide<sup>(64)</sup> will keep the solutions from changing color and maintain a fairly good clarity.

There has also been much research on the preparation of tablets. During the process of pill making and tablet compression, measures have been taken to prevent the introduction of foreign matter and impurities<sup>(65)</sup>. Research on adjunct material to be used with tablet preparations has experimented with starch and dextrinum to substitute for lactose<sup>(66)</sup>, and the quality of the prepared product meets specifications set down in the Pharmacopeia. When making aspirin compounds, the tablets were found to stick to their molds during the tablet compression phase and during store free salicylate acid was liberated. Changes have been made in compounding

the prescriptions and processing methods, so that there are no sticky molds and an increase in liberated salicylic acid is prevented(67). Some tablet preparations such as calcium p-aminosalicylate acid also have their disintegrating time limit shortened due to improvements in the prescription compound(68). In raising the tablet packaging efficiency, many techniques have been revolutionized. The invention of automatic tablet packaging equipment(69), the manually pushed tablet packaging machine(70), etc., are examples.

For adjunct materials used in the preparation of capsules, the pharmaceutical plants have experimented with beeswax and sugar as glycerine substitutes, and the prepared products have met basic requirements while saving a great amount of glycerine at the same time(71). Preparation of ophthalmic ointments(72) and eyedrops(73) under factory conditions in the pharmaceutical plants require special attention to the industrial process in order to assure the quality of the prepared product. Work in this field has received preliminary attention. Because of improvements in the preparation process, cough syrups are also fresh looking, sweet and pleasant to taste(74). During the course of storage, it is also easy for tincture preparations to become cloudy and liberate a sediment. After studies and tests, alcohol of a suitable concentration has been chosen as an extracting solvent and satisfactory methods of extraction and filtration are used, so that a first step is taken to improve the clarity of tincture preparations(75).

#### D. Changes in the Forms of Preparation of Chinese Traditional Drugs

The use of Chinese traditional drugs is seen in numerous ways and forms of preparation, and some of these reflect valuable experience. The preparation of Chinese traditional drugs in forms of pills, powders, ointments, spirits, potions, soups, waters, etc., have gained great confidence among the people, and it has solved the problem of treating sickness with medicines all these thousands of years. In order to develop this valuable heritage further so that its efficiency could be heightened, some improvements and changes must be made on the foundation of its original therapeutic value, so the drugs it covers could be better and easier to use. Changes in the forms of preparations must coordinate original theory, careful consideration of ancient methods of preparation and use the modern scientific method to study them and make changes.

For several years now, much work has been done in China on changing the forms of preparation. Some of it has concentrated on the separation of chemical components, while some of it has emphasized changes in prescription compounding. Engaged in such work are pharmaceutical plants located throughout the nation, the various schools and colleges of pharmacy, the great numbers of pharmacy workers, and other related units. In the pharmaceutical plants, research is conducted on one hand, while on the other, the production of new forms of preparation are being carried out. These products have been put on the market in a large area for trial use but systematic records of clinical observations as to their effectiveness are lacking. According to drug sales agencies everywhere and the response of the people, the new forms of preparations are effective and easy to use. Changed forms

of preparations with more definite results as to their effectiveness include coptis tablets, liver pills, locoweed antidote pills, etc., and new products are added every year. Other pharmaceutical plants have produced liquid extracts and other preparation forms from various kinds of single ingredient Chinese traditional drugs.

Most of the research on changes in the form of drug preparation has been directed toward drugs that have been most often used for years. According to the amount of each drug contained in the prescription, studies are made on their nature, either individually or collectively. Due to the fact that the pharmacology of many Chinese traditional drugs and their effective components is not understood, some generally recognized to be effective components such as organic acids, glucosides, volatile oils, saponin, alkaloids, coloring, bitterness, higher quality alcohols, etc., may be preserved during the refining process to be used as a rule to go by. Only the components in the crude drug such as starch, stearins, cellulose, etc., that definitely do not have any pharmacological effect are removed. Everything must be done to remove from the finished products the organic solvents that have been used during the refining process, but no preservatives are to be added.

Another method of changing the form of drug preparation is directed toward single ingredient Chinese traditional drugs through investigation of their drug components, studying methods of extraction and trying to establish standard for each type of preparation. Wherever a specifically special component such as an alkaloid, glucoside, saponin, or an anthraquinone derivative is found, this kind of component will be used as the criterion. Where chemical composition is not clear, the total solid is the criterion. In the selection of extraction solvents used in drug preparation, it will be based on the extraction rate of any particular substance.

Research on the forms of Chinese traditional drugs preparation is being carried out the various colleges and schools of pharmacy, hospital pharmacies, and other related research agencies throughout China. Most of this research involves testing and proving the definite therapeutic value of drug prescriptions against dysentery, hypertension, cirrhosis of the liver, cough and inflammation on the clinical level. Their research methods are generally alike, and most of them preserve the original prescription requirement as to drug dosage and preparation. There are two approaches in treating the drugs called for in the prescription. In one, the prescription drugs are treated together through mixing, decocting, or percolated and filtered extraction. In the other approach, individual treatment is given through selection of different extraction solvents or other extraction method in accordance with the components of the individual drugs. Take, for example, the broths of *Anemone chinensis*, Bunge and *Paeonia* that are used against dysentery<sup>(77)</sup>. By using these two methods, dry extracts have been prepared from these two medicines, and clinical trial has proved the same therapeutic effectiveness of both types of preparations. However, with the individual treatment method, suitable selection of solvent will remove more of the impurities and thus reduce the size of the preparation for convenient use. Most drug extracts tend to be sticky and moisture attracting which makes them hard to dry. Generally, they need to be dried under decreasing pressure in vacuum.

The double hsien broth, a prescription used to treat hypertension, is now converted to tablet preparations<sup>(78)</sup>. In its preparation, *Circuligo ensifolia*, R. Br., and *Epimedium macranthum*, Morr. et Dcne, are decocted together, the liquid is condensed into a dry powder with the spray drier and made into compressed tablets by the heavy pressure method. The spray dry method causes medicine liquids to dry rapidly so that the effective drug components are not damaged during the short period of heating. At the same time, the fine dry powder melts in water easily to release the drug effect. Broadened application of this drying method to conversions in the forms of drug preparation should be popularized.

The backache pill that has been used around the Hangchow area has been converted into a tablet preparation<sup>(79)</sup>. The original prescription contained 14 kinds of Chinese traditional drugs which included *Encommia ulmoides*, Oliv., *Ligusticum acutilobum*, S. et Z. According to drug composition or the total amount of matter to be extracted, alcohol of varying concentrations is used as the solvent to obtain extracts from the various drugs. The extract liquid is then condensed at temperatures below 80 C and made into granules for tablet compression after a suitable amount of filler such as starch, magnesium carbonate, etc., has been added to maintain dryness. The size of the tablet preparation is only 1/3 that of the original pill preparation. After clinical trial, its therapeutic effectiveness is found to be the same as that of the original preparation.

The relaxing powder compound<sup>(80)</sup> has been converted into a liquid extract type of preparation by coordinating the methods of individual treatment and collective treatment. This involves steam distilling the volatile components such as *Ligusticum acutilobum*, S. et Z., *Atractylis ovata*, Thunb., *Mentha*, raw ginger etc., to make an aromatic liquid and the distilled residue is mixed with *Bupleurum falcatum*, L., *Paeonia albiflora*, Pall., *Poria cocos* Wolf., licorice etc., and made into extract by using 15% alcohol as the solvent. The aromatic liquid is now added back to it to make each millilitre of compound comparable to 1 gram of the original drug. This preparation is effective in the treatment of anemia, shortness of breath, abdominal flatulence, and irregular menstruation in women.

At present, some results have also been obtained in conversion of the root preparation of *Strobilanthes flaccidifolius*, Nee.<sup>(81)</sup> which is used against parotitis. This root has been made into tablet preparations, syrups which have seen effective application. Furthermore, the effective components of the root of *Strobilanthes flaccidifolius*, Nees. has been studied and antibacterial tests have been made very the various extracts obtained. The tests have proved that this drug has an antibacterial effect toward many kinds of Gram negative and Gram positive bacteria.

Besides this, research on the preservation of decocted Chinese traditional drug preparations<sup>(82)</sup> proves better results with oxyquinoline sulfate which will prevent molds forming at a 0.05% concentration. With the exception of preservative action in a few individually decocted drugs, p-oxybenzoic esters and salicylaniline are not very effective as preservatives in most decocted preparations.

This article is compiled from material released in related journals throughout China and it may not be very comprehensive through possible omission of some reports. Furthermore, material published after May of this year has not been included due to the time element. For this, we beg your forbearance.

## VI. MAJOR ACHIEVEMENTS IN CHINESE PHARMACOLOGY

[Following is a translation of an article by Chin Yin-ch'ang, Sung Chen-yu, and Hsu Yu-chun in the Chinese-language periodical Chuang-chi I-k'an (Intermediate Medical Journal), Peiping, No. 10, October 1959, pages 16-18.]

During the past ten years, besides closely coordinating pharmacological production with product inspection and certifications, workers in pharmacology have concentrated their research efforts chiefly on chemotherapy and traditional Chinese drugs. The focus of chemotherapy has been directed toward erasing parasitical and infectious diseases, while pharmaceutical research of traditional Chinese drugs has been approached from several angles. These research efforts are now described in brief.

### Drugs for the Prevention and Treatment of Schistosomiasis

Based on various hunches and approaches, more than 1000 kinds of antimony compounds, compounds without antimony, and traditional Chinese drugs were synthesized and selected. It is found that antimony ammonium trigluconate, antimony sodium dithiosuccinate, antimony dithiopropionate, Sb11, complex salts of antimony quinine hydrochloride, para-amino-oxybenzene-heptane, rose phenylamine, and Cucurbita, Pepo, L. and wild daylily among the traditional Chinese drugs have a bactericidal effect on animals infected with schistosomiasis.

#### Clinical trials:

Antimony potassium trigluconate showed a satisfactory immediate and lasting therapeutic effect. Liver function was not seen to be impaired, and some slight change was noted in the T wave of the electrocardiogram. However, there was marked reaction in the intestinal tract with the appearance of rash and fever. Antimony sodium dithiosuccinate was given intramuscularly, and showed a greater recurrence rate than tartar emetic, though the side effects were comparatively lighter. The therapeutic effect of antimony dithiopropionate was marked; so was its toxicity. Oral antimony quinine hydrochloride showed a definite therapeutic effect. Cucurbita, Pepo, L. had the effect of increasing the therapeutic effectiveness of antimony potassium tartrate, showing definite results in clinical trial. Wild daylily showed a high therapeutic effect among the few patients it was tried on, but its recurrence rate was high as was its toxicity which caused blindness and swelling of the optic nerve. Its preparation taken orally with pills made from Bufo gargarizans and Glycyrrhiza glabra did not show any obvious toxic effect, and a definite therapeutic effect was observed. The toxicity of the other rose phenylamine drugs was generally great, and they have not been tried clinically.

The cathartic and diuretic effects of Lobelia radicans, Thunb., Diarrhena japonica, Lagenaria vulgaris, Phyllostachys puberula Monroe, etc., were also determined, and these drugs were found to be effective in treating ascites in late cases of schistosomiasis.

According to analysis of clinical figures, research on the toxicity of the antimony compounds shows the toxicity of antimony potassium tartrate to be related to sex, age, and air temperature. The state of thyroid function also affects the toxicity of the antimony compounds. Chlorpromazine may be used to control nausea from taking antimony potassium tartrate.

Much research has also been done on antidotes for the antimony compounds. It was discovered that thiouracil, procaine, and dithiosuccinate have the effect of lowering the toxicity of antimony potassium tartrate in white mice.

### Anthelmintics and Anti-malarial Drugs

#### 1. *Melia azedarach*

Margosin, the crystal extracted from it, has an anthelmintic effect. Its effect is the same as santonin when used for ascariasis. While it does not paralyze the roundworms rapidly, it does inactivate them after a period of time, and causes a portion of them to die. This anthelmintic effect has been determined clinically.

#### 2. *Quisqualis indica*, L.

The *Quisqualis indica* acid potassium salt is extracted and has been determined after clinical trials to have an anthelmintic effect, except that it evokes hiccups in the patient.

#### 3. *Orixa japonica*, Thunb.

The three kinds of alkaloids extracted from it - febrifugins A, B, and C - all show an anti-malarial effect. Comparison with the therapeutic value and toxicity of quinine shows: the antimalarial effect of febrifugin A to be equivalent to quinine, its toxicity 1.3 - 2.2 times that of quinine; the antimalarial effect of febrifugin B to be 89 - 122 times that of quinine, toxicity to be 134 - 154 times that of quinine; the antimalarial effect of febrifugin C to be 98 - 152 times that of quinine, toxicity to be 134 - 163 times that of quinine. All three types of febrifugin cause vomiting and without an effective method for counteracting it, clinical observation of their effectiveness has been difficult. At the same time, these three types of febrifugin can also lower the blood pressure of anesthetized animals, reduce the wavelength of heart contractions, and stimulate the pregnant uterus.

#### 4. *Brucea javanica*, L.

Experiments with malarial chickens have proved the antimalarial effect of this drug. During clinical trial, serious reactions such as nausea, vomiting, diarrhea affected therapeutic treatment. When its bitter extract was tried on malarial chickens, its antimalarial effect was noted with the serious toxicity resulting from the drug.

#### 5. Cyclochloroguanide

Its antimalarial effect within the body of the chicken is 10-40 times that of chloroguanide. In white mice, the toxicity of one oral dose is smaller than that of chloroguanide 7 - 10 times. Clinical trial shows it can control the recurrence of tertian, quartan, and malignant malaria completely.

## Antibacterial Drugs

### 1. *Coptis chinensis*

Its antibacterial effect has been determined at an early date. It has a bacteriostatic effect on most Gram positive and Gram negative bacteria. Recent experiments have shown that staphylococci resistant to penicillin are still sensitive to coptis. Not only is it therapeutically effective toward bacillary dysentery, but it also has an antiameba effect outside as well as inside the animal body. The *Bacillus flexneri* and the hemolytic streptococci both show drug tolerance to berberine. Nicotinic acid, vitamin B<sub>6</sub>, histidine, etc., show an obvious resistance to berberine.

### 2. Other antibacterial drugs

More than 500 kinds of traditional Chinese drugs have been screened and selected on the basis of their controlling effect toward *Staphylococcus aureus* and *Bacillus pyocyaneus*. It has been discovered that more than 20 kinds such as *Rhus javanica*, L., *Prunus mume*, S., Chinese redbud bark, violet, papaya, *Cornus officinalis*, etc., have a stronger antibacterial effect. Toward fungus, *Polygonatum giganteum*, Dietr var. Thunb., Maxim showed definite therapeutic value in the treatment of athlete's foot.

## Anti-neoplasm Drugs

In recent years, selection and research have also been carried out among traditional Chinese drugs, synthetic drugs, and antibiotics for their resistance against neoplasms. Actinomycin K extracted from a type of actinomycetes selected from the soil of China proves, after animal tests, its inhibiting effect on Ehrlich's carcinosarcoma ascites and other sarcomas. Its clinical value is being tested at the moment. Among the synthetic drugs, a tumorcidin that is effective against Ehrlich's carcinosarcoma ascites and several other kinds of sarcoma has also been found.

## Hypotensive Drugs

### 1. *China Rauwolfia verticillata*:

The plants grown in places such as Kwangtung (including Hainan Island), Kwangsi, Yunnan, etc., all belong to one type, and they are different from the India grown *rauwolfia* - *Ophiorrhiza japonica*, Blume. The reserpine content of the *rauwolfia* grown in these places varies. Besides reserpine, more than 40 kinds of alkaloids have been separated from them and they are different from the extracted foreign alkaloids. Given intravenously to drugged animals, *rauwolfia* A shows an obvious and lasting drop in blood pressure, the pulse slows down, pressure reaction on the carotid artery is lowered or lost, the pressure rising reaction of adrenalin is lowered or a pressure dropping reaction may be seen instead to show its adrenalin checking effect.

The acid based alcohol liquid extract and the complete alkaloid extracted from the leaves of *Rauwolfia verticillata* grown on Hainan Island show an obvious hypotensive effect on the experimented animals. When a dog with hypertension is given complete alkaloid from root of *rauwolfia* grown at the other places in smaller doses than that of complete alkaloid from the leaves, the blood pressure shows a very obvious drop and its effect is

stronger than a corresponding dosage of complete alkaloid from India grown rauwolfia. The complete alkaloid from the leaves of Haninan Island grown rauwolfia and roots of rauwolfia grown at the other locations have shown satisfactory results with clinical use. Furthermore, there are fewer side reactions in rauwolfia than in reserpine.

Complete alkaloid from root of rauwolfia grown on Hainan Island, when given in a dosage larger than usual after removal of reserpine, still show a pressure lowering effect.

## 2. *Veratrum nigrum*, L.:

There are many types of veratrum found growing in China. From these, the coarse extract from veratrum grown around Tien-mu Shan shows an obvious pressure lowering effect with animal tests. Pressure lowering effect of extracted Tien-mu veratrine B has definitely been established after tests.

## 3. Other hypotensive drugs:

After clinical observation, *Salsola ruthenica* shows a definite pressure lowering effect. The root and bark of *Paeonia moutan*, Sims. which is what is referred to among traditional Chinese drugs as moutan bark, single ingredient *Scutellaria baicalensis*, Georgi or compounds containing this ingredient all show a certain pressure lowering effect. Clinical results on the pressure lowering effect of *Encornia ulmoides*, Oliv., are inconclusive, though some researchers feel there is a definite therapeutic effect. Animal experiments show that *Conioselinum univittatum*, Turcz., also lowers the blood pressure. When used together with reserpine, it has a complementing effect. *Orixa japonica*, Thunb., grown near Hai-chou and *Inula Helinum* show definite therapeutic effectiveness after animal experiments and clinical trial.

## Cardiac Stimulants

### 1. *Strophanthus divaricatus* (Lour) Hook et Arn.:

It has a cardiac stimulating effect and its chief component is strophanthin *divaricatus* which is quite similar to k-strophanthin. Its effectiveness value is  $\frac{2}{3}$  that of k-strophanthin. Animal tests show an improvement in cardiac function, lowered venous pressure, increased per minute cardiac output, slowed pulse rate, better circulation, heightened myocardial stimulation, etc., and its increased use is seen in extrasystoles of the heart chambers. Clinical trial of this drug on cases of cardiac decompensation has shown satisfactory results. It must be noted, however, that the effect of strophanthin *divaricatus* on coronary arteries in generally administered doses is comparatively small, but overdosage will result in obvious contraction of the coronary arteries. There are indications at present that strophanthin *divaricatus* may be used as a k-strophanthin substitute on a clinical basis.

### 2. Bark of *Periploca sepium* (pei-wu-chia-pi):

Animal tests show that its defatted extract has an effect similar to that of strophanthin.

### 3. *Nerium indicum*, Mill.:

This also has a strong cardiogenic effect. Its effectiveness value is about one time that of digitalis. Its toxic reaction is similar to digitalis in often seen vomiting.

### Diuretics

#### 1. *Lobelia radicans*, Thunb.:

This has been used in late cases of schistosomiasis to treat ascites. Animal tests have proved that besides increasing the amount of urine passed, this drug also increases the chlorine volume to be eliminated. Before the diuretic effect is felt, the specific gravity of the blood is lowered, which proves that there is other diuretic control mechanism outside the kidneys. Besides this, it can also stimulate respiratory function by way of the carotid arteries through reflex action.

#### 2. *Akegia puinata*, Decen and *Poria cocos*, Wolf.:

Animal tests have proved that the diuretic effect of these two drugs is stronger than salyrgan.

#### 3. Kidney tea:

From animal tests, it has been proved that kidney tea, a successful diuretic that has passed its clinical tests shows the same effect as diamox.

### Expectorants

Tests have proved the effect of *Platycodon grandiflorum*, DC., *Peucedanum decursivum*, Maxim *angelica decursiva*, Mig., *Plantago major*, L. var. *asiatica*, *Aster tataricus*, L., *Gleditschia japonica*, Miq., *Arisaema japonicum*, Bl. on increasing the secretions of the animal respiratory passage.

### Drugs Which Act on the Uterus

#### 1. Ergot:

Since 1952, many types of wild growing ergot are found in China. The alkaloid content in most of them either meet or exceed requirements set down in the Pharmacopeia Sinica. At present, it is produced in volume for clinical use.

#### 2. *Ligusticum acutilobum* and *Leonurus sibiricus*:

After much research, it was proved that these two drugs have a stimulating effect on the uterus. The effect of *Ligusticum acutilobum* seem to be related to the physiology of the uterus. Before pressure is applied to the uterus, it causes a slight inhibiting action, but after pressure has been applied to the uterus, the drug causes the uterus to contract.

#### 3. *Narcissus tazetta*, L. and *Licoris radiata*, Herb.:

Both of these have a stimulating effect on the uterus.

### Drugs which Affect the Nervous System

#### 1. Analgesics:

*Corydalis ambigua*, Ah et Schl:

Animal tests have proved that the powder preparation, alcohol extract, water based extract of *Corydalis ambigua* all show a definite analgesic effect. The analgesic effect of corydaline B among the extracted

alkaloids is quite strong, second only to morphine. Corydaline A is the weakest, corydaline B is intermediate in strength. Tolerance to the drug may take place after two weeks of continuous use, its drug fastness being slower than morphine.

or *Cocculus diversifolius*, Miq.

The complete alkaloid and extracts of cocculin A, B, C all show an analgesic effect in animal tests. Among these extracts, cocculin C shows the strongest effect, though not as strong as that for the complete alkaloid. The toxicity of cocculin C is also greater and its effective dose is quite close to the toxic dose. It also exerts a strong stimulating effect on the nerve centers. A small dose will excite breathing, but a slightly larger dose may precipitate spasmodic convulsions, difficult breathing and death. Use of benadryl with it can heighten its analgesic effect. The analgesic action of cocculin A is greater than that of B, but increasing the dosage will result in an inverse effect instead. These three components also have a hypotensive effect. Besides this, cocculin A and B also resemble M - choline in effect.

Other analgesics:

Pain relieving prescriptions which have been handed down generation after generation in the practice of traditional Chinese medicine include aconite, *Datura alba*, Nees, *Scopolia japonica*, Maxim *Rhododendron sinense*, Sw, etc. Animal tests have proved the analgesic effect of aconitine and rhododendrine [7]. However, it is not as great as that of morphine. Scopolamine will increase the analgesic effect of rhododendrine, and slightly increase that of aconitine.

## 2. Antipyretics and Cough Sedatives

Pharmacological tests have proved the antipyretic effect of *Orixa japonica*, Thunb., *Scutellaria baicalensis*, Georgi, *Bupleurum falcatum*, L., *Siler divanictum*, *Pueraria thunbergiana* Benth, and *Artemesia capillaris*, Thunb. and the sedative effect of *Pinellia tuberifera*, Ten., and *Fritillaria verticillata*, Willd.

## 3. Nerve Center Stimulants

Animal tests have proved the nerve center stimulating effect of the cold liquid extract of *Illicium anisatum*, L., and found that its properties are quite similar to those of the *cocculus indicus* except more marked. This drug also has an awakening effect on amobarbital induced slumber, thereby lowering the death rate of poisoning by amobarbital.

## 4. Tranquillizers and Relaxants

In books on traditional Chinese medicine are recorded the use of bezoar for the treatment of convulsions. Animal tests have proved that bezoar can counteract convulsions induced by cocaine and caffeine. However, it could increase the phenobarbital induced death rate.

The convulsion preventive powder and its scorpion and centipede components used in traditional Chinese medicine practice have been found through animal tests to counteract convulsions induced by strychnine, nicotine, cardiazol, etc. However, it could not be used to counteract cocaine induced convulsions.

## 5. Drugs that Affect the Internal Organs and Reflexes

Animal tests have proved that vitamin B<sub>1</sub> can stimulate the chemical sensors in the small intestines, the extremities, the carotid artery and the aorta. It can also intensify the internal sensory reflexes caused by acetylcholines and para-nitro phenols. Prostigmine also increases the stimulating effect of acetylcholines on them.

Promizole, morphine lydol can affect the unconditional reflex. Corydaline B and reserpine can affect the conditional reflex.

When given in the right dosage, *Rhus javanica*, L. shows an obvious stimulating effect on higher nervous center activity and shortens the incubation period for conditional reflex factors pertaining to food and exercise in animals. It can also enliven the mental process.

## 6 Panax ginseng:

Toward the cerebral cortex, this drug intensifies the process of stimulation very obviously. Sometimes, there is also a very definite increase in the counteracting process of the cerebral cortex. A fluid extract preparation of ginseng can weaken cocaine caused excitement and convulsions. It can also be used to intensify the excitability process of related parts below the cerebral cortex.

Ginseng also has a blood sugar lowering effect. However, it is recognized that ginseng cannot substitute for insulin to correct the metabolism disturbance in diabetes of animals. It is surmised that its effectiveness takes place through the nervous system. Clinically, this drug may be used to complement treatment.

Ginseng is a tonic medicine often used by traditional Chinese medicine practitioners. Animal experiments with a dog weakened and critically ill through blood letting and asphyxiation show recovery with ginseng treatment. There are also reports that ginseng has a cardiotonic effect similar to other cardiac stimulants. It could also be used to prevent violent spasms of convulsions induced under high temperatures.

## Others

### 1. *Justicia gendassa* L.:

*Justicia gendassa* L. and *Sinomeninm acutum* are two drugs that the traditional Chinese medicine practitioner often used for treatment of rheumatic and painful joints. Their alkaloids are similar to the salicylates used for treating rheumatism, and it can lower the vitamin C content of the suprarenals.

### 2. *Glycyrrhiza glabra*, L.:

It has an effect similar to cortisone. Clinical trial reports that the use of *glycyrrhiza* liquid extract to treat Addison's Disease shows improving strength, increasing sodium content in blood serum, and rising blood pressure in patients. It is felt that the effect of hypoglycyrrhic

acid, one of its components, is similar to that of deoxycorticosterone. Therefore, clinical use of glycyrrhiza liquid extract to treat ulcers of the digestive tract shows side effects such as retention of blood sodium, lowering of blood sodium, rising blood pressure, edema of the lower extremities, etc. Besides this, animal experiments show glycyrrhiza to have an antidote effect on tetanus toxin. When used with oil of turpentine, its antidote effect is increased. This capacity to detoxify is possibly related to the function of the suprarenals.

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